HASAN AND SINGH
Intellectuals @ Law
Advocates, Patent And Trademark Attorneys

June 25, 2015

APPLICATION FOR COMPULSORY LICENCE UNDER SECTION 84 (1) OF THE PATENTS ACT, 1970

To,
The Controller of Patents
The Patent Office
Boudhik Sampada Bhavan
S. M. Road, Antop Hill
Mumbai-400037

E101/26783/2015-MUM
D-13852

Re.: Application for Compulsory Licence U/S 84(1) by Lee Pharma Limited in respect of Indian Patent No. 206543.

Dear Sir,

We, **Lee Pharma Limited**, the Applicant herein submit herewith an Application for Compulsory Licence u/s 84 (1) of The Patents Act, 1970 read with Rule 96 of The Patents Rules, 2003, along with necessary evidence available with us, the requisite form and the requisite fee.

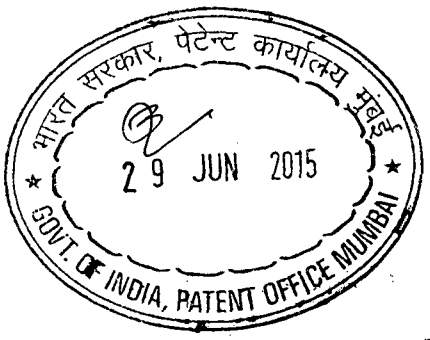
We hereby undertake to provide any additional documents as evidence as called for by the Controller or if necessary to support any of the averments made in the application.

We hereby request the Controller to take the application for Compulsory Licence along with the supportive documents on record and proceed in the matter and keep the Applicant informed about the each and every step taken in this matter. **Kindly send CBR and acknowledgement receipt to my email** ID- afzal@hasanandsingh.com and hasan@hasanandsingh.com

Furthermore, we request the Controller to give us an opportunity to being heard before the above application is disposed off.

Sincerely yours,

Afzal Hasan
of HASAN AND SINGH
Advocate and Patent Agent (IN/PA-1328)
For Lee Pharma Limited



Enclosures:

Original Power of Attorney
Form-17 (in duplicate)
A Cheque of Rs. 13,200/- towards prescribed official fee (Cq. No. 536749, SBH, 25/06/2015)
Application for Compulsory Licence and Supportive documents (Annexure) in duplicate

Flat No. 04, Sree Nilayam Apartment, Plot No. 12, Camelot Layout (Near Chirec Public School)
Kondapur, Hyderabad-500084, India
Phone: +91-40-65189786 , 23019786 Fax: +91-40-23013786
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Website: www.hasanandsingh.com

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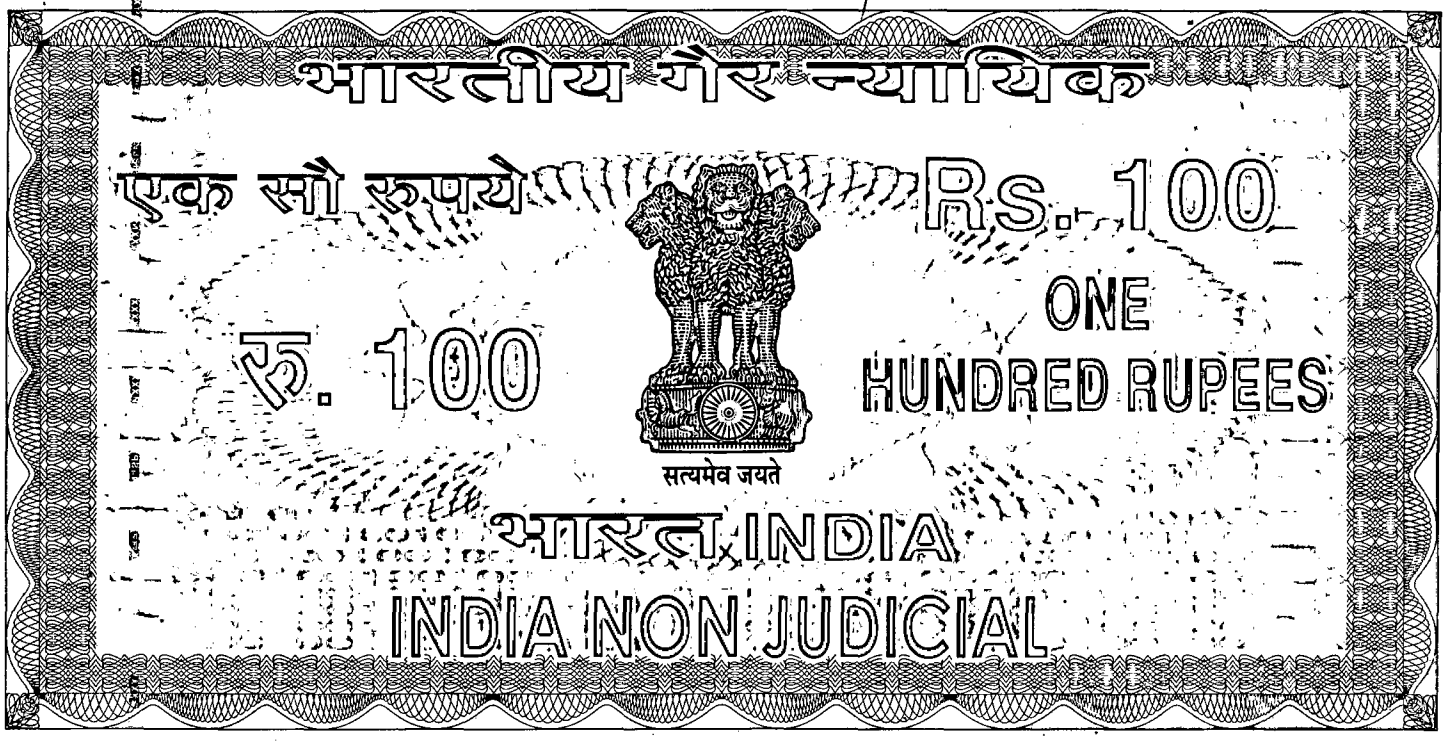

తెలంగాణ तेलंगाना TELANGANA B 911603

Date: 05/06/2015, 11:46 AM Serial No: 72,967 Denomination: 100

Purchased By:
S NAGESWARA RAO
S/O MALAKONDAIAH
R/O HYD

For Whom
LEE PHARMA LIMITED

200052627

Sub Registrar
Ex. Officio Stamp Vendor
SRO Ranga Reddy (R.O)

FORM 26
THE PATENTS ACT, 1970
(39 of 1970)
&
THE PATENT RULES, 2003
POWER OF ATTORNEY

We, LEE PHARMA LIMITED of the address: Sy. No. 257 & 258/1, Door No. 11-6-56, C Block, Opp. IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad-500037, India, do hereby authorize **Mr. Afzal Hasan, Ms. Vatsala Singh Hasan**, Advocate And/or Registered Patent Agent and all other Advocates And/or Registered Patent Agents, all Indian citizen, belonging to the firm HASAN AND SINGH of the address: Flat No. 04, Sree Nilayam Apartment, Plot No. 12, Camelot Layout (Near Chirec Public School), Kondapur, Hyderabad-500084, India, as our lawful Agent, to Act on our behalf for obtaining **Compulsory License** in respect of Indian **Patent No. 206543 (IN/PCT/2002/1154/MUM)** under the above mentioned Act, by preparing and filing necessary

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applications, making necessary payments, accepting receipts and in all matters and proceedings before the Controller of Patents or the Government of India in connection therewith or incidental thereto and in all matters or proceedings subsequent to the grant of such Compulsory License including attending hearings before the Controller of Patents or the Government of India thereof, filing affidavits, Forms, petitions or any other document in relation thereof, and in general to do all Acts or things (including appointment of a substitute Agent or substitutes, engage any consultant) as the said persons/Agents may deem necessary or expedient and request that all notices, requisitions and communications relating thereto in the matters and proceedings aforegoing be sent to such persons /Agent at:

HASAN AND SINGH
Flat No. 04, Sree Nilayam Apartment,
Plot No. 12, Camelot Layout (Near Chirec Public School),
Kondapur, Hyderabad-500084, India
Phone: +91-40-65189786, 23019786 / Cell: +91-9492033581
Fax: +91-40-23013786
E Mail: afzal@hasanandsingh.com / hasan@hasanandsingh.com

We hereby revoke all previous authorization in respect of same matter or proceeding.

We hereby assent to the action already taken, if any, by the said person(s) in respect of said matters and proceedings.

Dated this 19th day of June 2015.

Signature →

Name: **Venkata Reddy A.,**
Designation: Managing Director
LEE PHARMA LIMITED
Company seal:

LEE PHARMA LIMITED HYDERABAD

To
The Controller of Patents
The Patent Office
Mumbai, India

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FORM 17

200052628

THE PATENTS ACT, 1970
(39 of 1970)
&
THE PATENTS RULES, 2003
APPLICATION FOR COMPULSORY LICENCE
[*See* sections 84 (1), 91, 92(1) or 92A; rule 96]

We, **Lee Pharma Limited**, of the address Sy. No. 257 & 258/1, Door No.11-6/56-C, Opp. IDPL factory, Moosapet, Balanagar (Post), Hyderabad-500 037, India; hereby apply for the grant of a compulsory licence under Patent No. **IN 206543** (granted for patent application number IN/PCT/2002/01154/MUM) dated April 30, 2007 granted to **Bristol-Mayers Squibb Company (BMS)** of Lawrenceville-Princeton Road., P.O Box 4000, Princeton, New Jersey 08543-4000, USA, for which the patentee is **AstraZeneca AB** of the address SE-151 85, Sodertalje, Sweden on the following grounds namely:-

(a) that the reasonable requirements of the public with respect to the patented invention have not been satisfied; ***and***

(b) that the patented invention is not available to the public at a reasonably affordable price; ***and***

(c) that the patented invention is not worked in the territory of India.

We declare that the facts and matters stated herein are true to the best of our knowledge, information and belief.

The details of documentary evidence in support of our interest and grounds stated above are given below:

- **as enclosed herewith.**

Our address for service in India is -

HASAN AND SINGH
Flat No. 04, Sree Nilayam Apartment,
Plot No. 12, Camelot Layout (Near Chirec Public School),
Kondapur, Hyderabad-500084, India
Phone: +91-40-65189786, 23019786 / Cell: +91-9492033581; Fax: +91-40-23013786
E Mail: afzal@hasanandsingh.com / hasan@hasanandsingh.com

Dated this 25th day of June 2015 E-77/1/2015-MUM

Afsar Hasan.

13200 | रूपये नकद/चेक/मनी ऑर्डर द्वारा
CBR संख्या 9894 ..दि. 29/06/15
के तहत प्राप्त हुए।

Afzal Hasan
of HASAN AND SINGH
IN/PA-1328
Advocate And Patent Agent
for Lee Pharma Limited

To,
The Controller of Patents,
The Patent Office,
Mumbai, India.

रौफडिया

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E-101/26285/2015

200052629

BEFORE THE CONTROLLER OF PATENTS, MUMBAI

IN THE MATTER OF THE PATENTS ACT, 1970
(AS AMENDED BY THE PATENT AMENDMENT ACT, 2005)
AND
IN THE MATTER OF PATENTS RULES, 2003
(AS AMENDED BY THE PATENT RULES, 2014)
AND
IN THE MATTER OF
APPLICATION UNDER SECTION 84(1) OF THE PATENTS ACT, 1970 (AS AMENDED) FOR GRANT OF COMPULSORY LICENCE ON PATENT NO. 206543 DATED APRIL 30, 2007

Lee Pharma Limited ..... **APPLICANT/PETITIONER**

VERSUS

AstraZeneca AB ..... **RESPONDENT/PATENTEE**

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BEFORE THE CONTROLLER OF PATENTS
MUMBAI

IN THE MATTER OF THE PATENTS ACT, 1970 (AS AMENDED BY THE PATENT AMENDMENT ACT, 2005)

AND

IN THE MATTER OF PATENTS RULES, 2003 (AS AMENDED BY THE PATENT RULES, 2014)

AND

IN THE MATTER OF

APPLICATION UNDER SECTION 84(1) OF THE PATENTS ACT, 1970 (AS AMENDED) FOR GRANT OF COMPULSORY LICENCE

IN THE MATTER OF

PATENT NO. 206543 DATED APRIL 30, 2007

LEE PHARMA LIMITED

.....APPLICANT/PETITIONER

VS

ASTRAZENECA AB

..... RESPONDENT/PATENTEE

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We, **Lee Pharma Limited**, of the address: Sy. No. 257 & 258/1, Door No.11-6/56-C, Opp. IDPL factory, Moosapet, Balanagar (Post), Hyderabad-500 037, India; hereby apply for the grant of a Compulsory Licence under Patent No. **IN 206543** (granted for patent application number IN/PCT/2002/01154/MUM) dated April 30, 2007 granted to Bristol-Mayers Squibb Company (BMS) of Lawrenceville-Princeton Road., P.O Box 4000, Princeton, New Jersey 08543-4000, USA, for which the patentee is AstraZeneca AB of the address: SE-151 85, Sodertalje, Sweden on the following grounds namely:-

(a) that the reasonable requirements of the public with respect to the patented invention have not been satisfied; ***and***

(b) that the patented invention is not available to the public at a reasonably affordable price; ***and***

(c) that the patented invention is not worked in the territory of India.

1. **About the Applicant/Petitioner:**

The applicant herein is a company incorporated under the Indian Companies Act, 1956 having its principal place of business at Sy. No. 257 & 258/1, Door No.11-6/56-C, Opp. IDPL factory, Moosapet, Balanagar (Post), Hyderabad-500 037, India. The Applicant Company was incorporated in the year 1997, and since last more than 17 years, it has been involved in research and development, production, distribution, sales, marketing and export of pharmaceutical products, pharmaceutical formulations, intermediates and APIs. Presently the Applicant Company's products are sold in India and exported to more than 48 countries worldwide and are known and appreciated for their

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quality and economical cost. The Applicant is an ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP 100% EOU Certified Company and one of the largest manufacturers of Bulk Drugs & Intermediates in India having three manufacturing units situated in Hyderabad and Vishakhapatnam, India.

The Applicant has State-of-Art Research and Development centre and highly dedicated and experienced team of senior scientists who are consistently and extensively involved in R&D activities and have developed many novel processes, compounds and intermediates. The Applicant is spending high amount of money in R&D activities every year and has filed many patent applications for the processes, intermediates and compounds which are developed by it.

The Applicant has also received award for Excellence in Research and Development from The Federation of Andhra Pradesh Chambers of Commerce and Industry (FAPCCI). Its in-house R&D unit is recognized by Department of Scientific and Industrial Research (DSIR), Ministry of Science and Technology, Govt. of India. Additionally the Applicant is one of the biggest bulk drug manufacturer and suppliers for a large number of pharmaceutical companies in India and has a network of strong marketing team with PAN India presence and grass root penetration in urban and rural Indian market.

2. **Subject matter of the present application:**

The present application is for grant of Compulsory Licence (CL) for manufacturing and selling of the product (compound) called "**SAXAGLIPTIN**" in India, which is protected and covered by Indian Patent No. **206543** titled **"A CYCLOPROPYL-FUSED PYRROLIDINE-BASED COMPOUND"**, granted on April 30, 2007,

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to **M/S Bristol-Mayers Squibb Company (BMS)** (the grantee) of USA for a Patent term of 20 years from 5th March 2001. A copy of the Indian Patent No. 206543 granted on April 30, 2007 is annexed herewith as **Annexure-A**. By virtue of an Assignment Deed submitted in Indian Patent Office on April 03, 2014, BMS (Grantee) has transferred/assigned the ownership rights in the Indian Patent No. 206543 to **AstraZeneca AB (Patentee/Assignee)** of the address SE-151 85, Sodertalje, Sweden. A copy of the Assignment Deed signed by BMS (the grantee/assignor) and AstraZeneca AB (the patentee/assignee) is annexed herewith as **Annexure-B.**

The said product "**SAXAGLIPTIN**" is marketed and sold in India by AstraZeneca AB in tablet dosage form as a single active agent under the brand name "**ONGLYZA**" (strengths 2.5 mg and 5 mg) and also in combination with Metformin under the brand name "**KOMBIGLYZE XR**" (strengths 5/500 mg and 5/1000 mg). Saxagliptin is a dipeptidyl peptidase-4 (DPP4) inhibitor prescribed for the treatment of Type-II diabetes mellitus (DM). Currently the prices of ONGLYZA and KOMBIGLYZE XR in India are as shown in below table-

BRAND	**Cost/Strip**	**Cost/Tablet**	**Monthly Cost (30 days)**
ONGLYZA 2.5 mg	Rs. 605/- (14 Tablets)	Rs. 43.21/-	Rs. 1296.42/-
# ONGLYZA 5 mg	Rs. 581/- (14 Tablets)	Rs. 41.5/-	Rs. 1245/-
KOMBIGLYZE XR (5/500 and 5/1000 mg)	Rs. 343/- (7 Tablets)	Rs. 49/-	Rs. 1470/-

Currently, old stock is available in the market. Whereas, price is expected to be increased with arrival of new batch in the market.

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ONGLYZA or KOMBIGLYZE XR is prescribed as once daily therapy.

(Copies of product labels of ONGLYZA (2.5 mg and 5 mg) and KOMBIGLYZE XR (5/500 mg and 5/1000 mg) are annexed herewith as **Annexure-C.**

3. DIABETES MELLITUS

- **The Disease**

Diabetes Mellitus (DM) is a chronic disease which occurs when the pancreas does not produce enough insulin (Type-I DM) or when the body does not effectively utilise the insulin produced by pancreas (Type-II DM), leading to increased concentration of glucose in the blood (hyperglycaemia). DM is one of the most common chronic diseases across the world and the number of diabetic patients is on rise. The complications related to diabetes pose a significant health care burden and a deterrent to overall quality of life. The prevalence of Type-II DM is increasing worldwide, particularly in developing countries. According to one recent study, number of patients suffering from diabetes in India has increased 123% since 1990. Over 90% diabetic patients are suffering with Type-II DM.

- **Key Statistics**

According to International Diabetes Federation (IDF) (Source: IDF DIABETES Atlas 6th edition, 2014 update annexed herewith as **Annexure-D**):

- There were 387 million people in 2014 living with diabetes worldwide with a prevalence of 8.3% globally, wherein 168.73 million (43.6%) were remained undiagnosed.

- Expected to rise to 592 million by 2035 with an increase of about 53%.
- 77% people with diabetes live in low-income and middle-income countries.
- 4.9 million deaths in 2014; in every 7 seconds, 1 person dies due to diabetes.

According to WHO (Source: WHO FACT FILE, http://www.who.int/features/factfiles/diabetes/facts/en/, annexed herewith as **Annexure-E):**

- Diabetes is predicted to become the 7th leading cause of death in the world by the year 2030.
- Cardiovascular disease is responsible for between 50% and 80% of deaths in people with diabetes.
- In 2012 diabetes was the direct cause of 1.5 million deaths.
- 80% of diabetes deaths occur in low- and middle-income countries.
- Diabetes is a leading cause of blindness, amputation and kidney failure.
- Type-II DM accounts for around 90% of all diabetes worldwide. Reports of Type-II diabetes in children – previously rare – have increased worldwide.
- Diabetes is a leading cause of blindness, amputation and kidney failure.

4. POSITION OF DIABETES IN INDIA

According to Indian Council of Medical Research–INdiaDIABetes (ICMR–INDIAB) study, in 2011 the number of people with diabetes was 62.4 million and the number of people with pre-diabetes was 77.2 million. (**Source:** Diabetologia (2011) 54:3022–3027; DOI 10.1007/s00125-011-2291-5, annexed herewith as **Annexure-F**).

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According to International Diabetes Federation (IDF), 2014 update (**Annexure-D**),

- there were 66.84 million diabetic people in India in 2014 with a national prevalence of 8.63%;
- 35.49 million (53.09%) were remained undiagnosed;
- there was 1039980 numbers of deaths (people with age 20-79) due to diabetes in 2014;
- below China, India remains in the second position of top ten countries having highest number of diabetic people.
- in 2014, the cost of diabetes treatment in India per person was 94.96 USD (equivalent to about 6018 Indian Rupees).

5. TREATMENT AND ECONOMIC BURDEN

Type-II DM is a chronic condition that affects the way our body metabolizes sugar (glucose) either by resistance of our body to effects of insulin. There's no cure for type-II DM. The disease gets worse over time. The disease condition is managed by diet, exercise and medication to achieve the target level of sugar in the blood. Initially medication starts as tablet with single drug which latter may shift to combination of tablets/medications.

There are different types of oral drugs available for treatment that work in different ways to lower the blood glucose level such as Sulfonylureas, Biguanides, Meglitinides, Thiazolidinediones, DPP-4 inhibitors, SGLT2 Inhibitors, Alpha-glucosidase inhibitors and Bile Acid Sequestrants.

SAXAGLIPTIN is a dipeptidyl peptidase–4 (DPP4) inhibitor for the treatment of Type IIDM in adults which is not associated with weight gain.

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Source: The above information has been collected from following sources, copies of which are annexed as **Annexure-F**, **Annexure-G**, **Annexure-H** and **Annexure-I**:

Annexure-G: A print out of the hyperlink to mayo clinic: http://www.mayoclinic.org/diseasesconditions/type2diabetes/basics/treatment/con20031902?p=1

Annexure-H: A print out of the hyperlink to mayo NHS: http://www.nhs.uk/Pages/Preview.aspx?site=Diabetestype2&print=635658022118401934&JScript=1

Annexure-I: A print out of the hyperlink to American Diabetes Association: http://www.diabetes.org/livingwithdiabetes/treatmentandcare/medication/oralmedications/whataremyoptions.html

Diabetes Mellitus is a growing epidemic and the cost of treating diabetes is largely increasing. In a study performed at Chennai, the annual mean direct cost for each person with diabetes was estimated to be Indian Rupee (INR) 23,818; in which INR 22, 720 (95% of total cost) spent on medicines (Source: Journal of Diabetology, October 2013; 3:4; annexed herewith as **Annexure-J**).

In 2014, the cost of diabetes treatment in India per person was 94.96 USD (equivalent to about 6018 Indian Rupees). (Source: **Annexure-D**).

According to WHO, diabetes is a costly disease, not only for the affected individual and his/her family, but also for the health authorities. Studies in

India estimate that, for a low-income Indian family with an adult with diabetes, as much as 25% of family income may be devoted to diabetes care. (Source: http://www.who.int/mediacentre/factsheets/fs236/en/ , a print out of the hyperlink is annexed herewith as **Annexure-K**).

As stated, 77% people with diabetes live in low-income and middle-income groups and 80% of diabetes deaths occur in low- and middle-income countries. India is a lower middle income country with a population of around 1.3 billion wherein there are 66.84 million diabetic people and more than 77 million pre-diabetic people. Further the Type-II DM is now shifting to younger age groups and the takeoff point of prevalence of diabetes occurring at the age of 25 – 35 years in India causes huge burden on the patient and his/her family.

Therefore in a country like India, where majority of the population is poor and cannot afford costly medicines, the price of life saving medicines which are required to be taken on daily basis for lifelong for disease like diabetes is very crucial.

6. SAXAGLIPTIN AND DIABETES

ONGLYZA (Saxagliptin) is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which is prescribed as an adjunct to diet and exercise to improve glycemic control in adults with Type-II diabetes mellitus in multiple clinical settings at a dose of 2.5 mg or 5 mg once daily taken regardless of meals. Saxagliptin is not associated with increased body weight. (Source: ONGLYZA package insert annexed herewith as **Annexure-L**)

Saxagliptin is also prescribed in combination with Metformin for use as an adjunct to diet and exercise to improve glycemic control in adults with Type-II DM who are inadequately controlled on metformin alone. Such

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combination is available under brand name KOMBIGLYZE XR (Saxagliptin + Metformin HCl; strength 5/1000 mg and 5/500 mg) as extended release tablet. (Source: KOMBIGLYZE XR package insert annexed herewith as **Annexure-M**).

7. THE PATENTEE AND SAXAGLIPTIN

Working of Patent in India

It is submitted that, even after passing of eight years from the date of grant of above identified Indian Patent No. 206543 covering the compound Saxagliptin; there is limited availability of Saxagliptin in India and still Saxagliptin tablets (ONGLYZA / KOMBIGLYZE XR) are not available to the general public at reasonably affordable price; and thereby reasonable requirements of general public has not been met which is further explained in below paragraphs.

Product NOT Manufactured in India

- It is submitted that, **even after eight years** of grant of the Indian Patent 206543 to Bristol-Mayers Squibb Company the compound **Saxagliptin is still not manufactured by the Grantee or Patentee in India**; rather it is imported to India by BMS or AstraZeneca AB and marketed in India by AstraZeneca AB.

Product Imported, import cost and MRP in India

- Based on the information submitted in Form-27 for the Calendar Year 2013, submitted in February, 2014 by the grantee (BMS) with respect to working of patent in India; Saxagliptin is not manufactured in India. All forms of Saxagliptin (tablet/API) have been imported by BMS from foreign countries (Ireland and USA) to India. The figures submitted in Form-27 (for 2013) are as follows:

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Country	Product	Quantum	Value (Rs)
Ireland	ONGLYZA	700,078	541,778
USA	KOMBIGLYZE	123,777	112,851
Total		**823,855**	**654,629**

- Copy of Form-27 submitted for the Calendar Year 2013 is annexed herewith as **Annexure-N**.

- Here it is to be noted that "Quantum" is not fully expressed and is unclear i.e. to say "What quantum represents?" However, under general understanding, it can be perceived that the quantum refers to the number of tablets.

- Saxagliptin is imported to India in finished dosage (tablet) form in packaged form. If we consider quantum in terms of number of tablets, then the total number of tablets (both ONGLYZA and KMBIGLYZE) for the whole year (2013) was **823,855** and total values was **Rs.654,629/-.**

- Based on above consideration, **cost of importing one tablet of ONGLYZA in India is only about Rs. 0.80** (per tablet price).Whereas, same tablet is being sold in Indian market by BMS and AstraZeneca at a market price of about Rs. 41-45/- per tablet. Similarly cost of importing one tablet of KOMBIGLYZE in India only about Rs. 0.92 (per tablet) but the same tablet is being sold in Indian market at a price of Rs. 49/- per tablet. This clearly demonstrates the monopoly of patentee and high price of the tablet despite a small amount of cost incurred in manufacturing/importing

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a single tablet. The patentee/assignee is making a high percentage of profit by increasing the product price, which is directly affecting the affordability of Indian diabetes patients who cannot afford high price for their treatment.

Product Exported

A website named www.zauba.com, provides product import and export data online for India. Extracting the export data for Saxagliptin, it has been shown that, a large quantity of Saxagliptin (includes ONGLYZA, KOMBIGLYZE and SAXAGLIPTIN HCl) has been exported to foreign countries, wherein United Kingdom is the destination with majority of times.

By analysis of the all saxagliptin export data (up to date 27-05-2015) in the tool provided in the website, it reveals that, "India exported saxagliptin worth USD 3,696,275 with total quantity of 4,354. Canada is the largest buyer of Saxagliptin accounting for exports worth USD 2,217,381 followed by Slovenia and United States which imported Saxagliptin worth USD 828,386 and USD 502,240 respectively."

Further the graphical representation of the Saxagliptin export data shows that, in terms of quantity, Mauritius imported 53.1%, United Kingdom imported 21.7% and USA imported 11.4%.

This analysis reveals that following surprising facts-

(i). Even after eight years of grant of the Indian Patent, Saxagliptin is not been manufactured by the Grantee / Patentee within the territory of India;

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(ii). Saxagliptin and Saxagliptin + Metformin combination is imported in India by the Grantee / Patentee at a cost as low as **less than one Rupee** per tablet;

(iii). Same tablet is sold by the Grantee / Patentee to Indian patients at a price as high as Rs. 41-45 per tablet;

(iv). Quantity of the imported tablets it too less to meet the requirements of Indian Patients suffering from Type-II Diabetes Mellitus (as per Form-27 data);

(v). Whereas, the import of the tablets in India itself is too less to meet the Indian requirements, a majority of the imported medicine is again being exported back to foreign countries making this medicine virtually unavailable to Indian patients.

Copies of printout from the web linkhttps://www.zauba.com/exportanalysis-saxagliptin-report.html and https://www.zauba.com/export-saxagliptin-hs-code.htmlhave been annexed herewith as **Annexure-O**.

Product Availability to Indian Type-II DM Patients:

- Statistical figures show that, currently there are nearly about 60.1 million (90% of total 66.84 million diabetic people) people in India suffering from Type-II Diabetes Mellitus, Other major compounds currently available in the Indian market in the DPP-4 inhibitors category include Linagliptin (Trazenta), Sitagliptin (Januvia) and Vildagliptin (Glavus). Thereby, including Saxagliptin, these are the four key medicines which are used for the treatment of Type-II Diabetes Mellitus.

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- Considering the lowest requirement for Saxagliptin, if it was assumed that other three medicines above were prescribed to even 90% of the patients suffering from Type-II Diabetes Mellitus and only 10% patients were prescribed Saxagliptin, still 6 million people would require Saxagliptin.

- However, even if only one million out of 60.1 million Type-II DM patients are prescribed Saxagliptin medication, then the total number of tablets required for one patient in a once daily in one year would be 365 tablets/ per year.

  Accordingly, for one million patients it can be calculated as-

  1,000,000 (one Million) x 365 = 365,000,000 tablets/year.

- As per Form-27 data, the total number of tablets (both ONGLYZA and KMBIGLYZE) for the whole year (2013) was 823,855; which is about **0.23%** of the total number tablets required for a year. **Thus, there is more than 99% shortage of Saxagliptin in the Indian market**.

8. CONCLUSION

From the above mentioned data and analysis, the Applicant submits that:

(a) **Invention not worked in India**- even after passing a long period of about eight years from the date of grant (granted on April 30, 2007), the patentee has not taken adequate steps to manufacture Saxagliptin in India and make full use of the invention in India;

(b) **Not available at a reasonably affordable price**- cost of importing one tablet of ONGLYZA in India is only about **Rs 0.80 /per tablet**.

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Whereas, same tablet is being sold in Indian market by BMS and AstraZeneca at a market price of about **Rs. 41-45/- per tablet**. Similarly cost of importing one tablet of KOMBIGLYZE in India only about **Rs. 0.92/ per tablet** but the same tablet is being sold in Indian market at a price of **Rs. 49/- per tablet**.

In a poor country like India where according to the recent reports of Rangarajan committee about 30% of the total population lives below poverty line which earns even **less than Rs. 32/- per day** in rural areas and **less than Rs. 47/- per day** in urban areas, the cost of one tablet of Patentee's medicine is even more than their whole day earning. Therefore, excessive high price of the medicines sold by Grantee/ Patentee in Indian market is a barrier to access of Saxagliptin for the poor patients of India. Thereby the reasonable requirement of public is not being met in terms of reasonably affordable price;

(c) **Reasonable requirement of the public not satisfied-** the public requirement of the patented product (saxagliptin) is not being met; since there is more than 99% shortage of Saxagliptin in the market.

9. APPLICANT'S INTEREST

The Applicant herein is a pharmaceutical company involved in research and development, production, distribution, sales, marketing and export of pharmaceutical products, pharmaceutical formulations, intermediates and APIs for more than 17 years and sells its products in India as well in more than 48 countries worldwide.

Applicant's Motive for grant of Compulsory Licence:

Being in the field of pharmaceutical business, the applicant can understand the socioeconomic status and difficulty faced by Indian

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diabetic patients and also the burden of diabetes to India at this growing trend of the disease. One of the strong reasons to inaccessibility to medicine to save their lives or improve to a better life, is the **cost incurred in medication**, as majority of Indian diabetic people belong to poor families where they can't afford the medication. Another strong reason pertaining to inaccessibility to Saxagliptin is **unavailability of the product in the Indian market**. In the aim of serve to the Indian public to improve the access to the medication in each part of the country, the Applicant has decided to offer the medication ONGLYZA and KOMBIGLYZE in a lowest possible price that can be easily accessible to them in reasonably affordable price and in a sufficient quantity in terms of number of tablets to fulfil the public demand.

10. APPLICANT'S CAPABILITY

As stated earlier in above paragraphs, the Applicant **LEE PHARMA LIMITED** is a leading pharmaceutical company catering the needs of Indians and world also. The company has been serving India for more than 17 years. The applicant has its own R&D. Applicant also have a network of strong marketing team with PAN India presence and grass root penetration in urban and rural Indian market through its network.

State-of -Art R&D and its Recognition:

The Applicant submits that it has State-of-Art R&D centre where highly dedicated and experienced team of senior scientists has been involved in R&D activities and they have developed many novel process, compounds and intermediates. It has filed many patent applications for the processes, intermediates and compounds. A copy of list of patent applications filed by the Applicant is annexed herewith as **Annexure-P.** The Applicant's in-house R&D unit is recognized by Department of Scientific and Industrial Research (DSIR), Ministry of

Science and Technology, Govt. of India and has also received award for Excellence in Research and Development from The Federation of Andhra Pradesh Chambers of Commerce and Industry (FAPCCI). Copies of certificates of recognition of R&D unit and award certificate are annexed herewith as **Annexure-Q**.

Manufacturing Facilitates for Saxagliptin:

The applicant currently produces a large number of APIs and intermediates, including intermediates for Saxagliptin, a copy of which is annexed herewith as **Annexure-R**. With regard to manufacture Saxagliptin the Applicant submits that, it has developed the technology, infrastructure and facilities for industrial scale preparation of DPP4 inhibitor compound Saxagliptin. The Applicant has developed the capabilities to manufacture and sell Saxagliptin both as API and in tablet form. The Applicant is an ISO 9001: 2008, ISO 14001:2004, EU GMP & WHO GMP 100% EOU Certified Company, currently having three manufacturing units situated in Hyderabad and Vishakhapatnam, India. Certification/approval details of our manufacturing facilities and products are annexed herewith as **Annexure-S**.

The Applicant has also applied for Drug Licence before the Drug Controller Administration, Govt. of Telangana to manufacture Saxagliptin tablets along with combination tablets of Saxagliptin and Metformin. A copy of the application duly acknowledged by the Licensing Authority is annexed herewith as **Annexure-T**.

Applicant's Production Capability:

The Applicant has the capacity to manufacture Saxagliptin and Saxagliptin + Metformin tablets @ **10,00,000 tablets/day**; Therefore,

applicant is capable of fulfilling the requirements of the country and satisfy the requirements of the public of India.

Ability of the Applicant to market the product:

The Applicant has the abilities and capabilities to manufacture and market the product Saxagliptin to fulfil the need of the entire diabetic patients of the nation. With its existing PAN India network of associates and representatives, applicant is capable of making the product available across the country to the patients in all rural and urban areas of the country.

Proposed Price:

The cost proposed by the Applicant

- for Saxagliptin 2.5 mg and Saxagliptin 5 mg are as follows:

Product	Strength	Price/Strip of 14 Tablets (MRP in Rs.)	Price/Unit Tablet (MRP in Rs.)
Saxagliptin	2.5 mg	Rs. 378.00	Rs. 27.00
Saxagliptin	5 mg	Rs. 406.00	Rs. 29.00

- for Saxagliptin + Metformin (mg/mg) are as follows:

Product	Strength	Price/Strip of 7 Tablets (MRP in Rs.)	Price/Unit Tablet (MRP in Rs.)
Saxagliptin + Metformin XR	5/500 mg	Rs. 210.00	Rs. 30.00
Saxagliptin + Metformin XR	5/1000 mg	Rs. 220.50	Rs. 31.50

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11. EFFORTS MADE BY APPLICANT FOR VOLUNTARY LICENCE

The Applicant independently tried the best with full efforts to make a deal with the Patentee and obtain a voluntary licence from the Patentee to manufacture and sell the product Saxagliptin covered by Indian Patent No. 206543 both as API and in tablet formulation as well as tablets of Saxagiptin + Metformin combination in India. Such effort and request for licence had been made by the Applicant by virtue of request letter dated **May 02, 2014**. In response to the said request for licence, the Patentee vide letter dated **June 02, 2014** sought certain clarifications about the Applicant company (Lee Pharma Limited) at the same time disagreed to the Applicant submission that, "*the Saxagliptin tablets (ONGLYZA) are not available to the general public at reasonably affordable price and thereby the reasonable requirements of the general public is not being met*". However, this reply was sent by the Patentee via email which could not be received by the Applicant. Therefore, on 31st October 2014, Applicant sent a reminder to the Patentee with request to reply to its licence request. In response to his reminder, on November 07, 2014, Applicant received a reply from Patentee's counsel Anand And Anand, asking for clarifications, Applicant's manufacturing and marketing details, it's R&D status and all relevant details. Applicant promptly replied on **November 22, 2014** providing all information and clarifications sought by the Patentee. On January 02, 2015, Applicant received one email from Patentee's counsel Anand And Anand with acknowledgement of receipt of the documents and with promise to revert soon. On January 17, 2015, Applicant sent one reminder request to the Patentee's counsel with request to revert with Patentee's views on Applicant's licence request but Applicant did not receive any reply neither from the Patentee nor from their counsel. The Applicant awaited for more than a month to

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receive any affirmative reply, but neither Patentee nor their counsel made any reply. Subsequently the Applicant's counsel in an email dated March 02, 2015requested to Patentee's counsel to reply to the Applicant's licence request and inform if they required any further information but again did not receive any reply from them. Since this last request sent by the Applicant's counsel, more than three months have passed but yet neither the Patentee nor their counsel and conveyed their reply to the Applicant's licence request and they have become completely non-responsive. Due to this non-responsive approach and in the *bonafide* efforts by Applicant, more than one year has already passed from the date of voluntary licence request.

Thus the applicant failed to get voluntary licence as the Patentee stayed mute in this matter to discuss whatsoever despite our repeated efforts to get Patentee's views regarding the issuance of voluntary licence to manufacture and sell the product in India. Copies of letters/emails communicated between Applicant and the Patentee are annexed herewith in **Annexure-U**. All the above communications, made between the Applicant and the Patentee are listed in the below table in chronological order:

Date	Letter/Communication by	Description
May 02, 2014	Applicant (Lee Pharma Limited)	Requested for Voluntary Licence
Oct. 31, 2014	Applicant (Lee Pharma Limited)	Requested to reply to its licence request
Nov. 07, 2014	Patentee's Counsel (ANAND & ANAND)	Replied with Patentee's response dated June 02, 2014
	June 02, 2014 - Patentee sought clarifications about Applicant company via email which could not be received by the Applicant (Lee Pharma)	

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Nov. 22, 2014	Applicant (Lee Pharma Limited)	Provided clarifications about company and complete details and evidences of all required information and details
January 02, 2015	Patentee's Counsel (ANAND & ANAND)	Acknowledged receipt of 22nd Nov. Letter of Applicant and promised to revert soon
January 17, 2015	Applicant (Lee Pharma Limited)	Requested to reply with Patentee's views on licence request but did not receive any reply
March 02, 2015	Applicant's Counsel (HASAN AND SINGH)	Requested to reply with Patentee's views but did not receive any reply
	No further reply from Patentee till date.	

12. GROUNDS FOR COMPULSORY LICENCE

The Applicant submits that in view of above facts and submissions described above, a prima facie case that the reasonable requirements of the public not being satisfied and a grant of compulsory licence is made out because:

(a) **Voluntary licence not granted-** the Applicant herein had made a request to the Patentee for voluntary licence to which the Patentee initially sought for clarifications about the Applicant company and at the same time denied the Applicant's submission that "*the Saxagliptin tablets (ONGLYZA) are not available to the general public at reasonably affordable price and thereby the reasonable requirements of the general public is not being met*"; and despite repeated reminders to the Patentee or it's counsel, the Patentee neither provided its views regarding the issuance/refusal of voluntary licence nor shown any interest to discuss in this matter

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and on account thereof, establishment of a new trade or industry for supply of Saxagliptin is deeply hampered;

(b) **Reasonable requirement of the public not satisfied**- as described above, the quantity of Saxagliptin supplied by the Patentee in the market only fulfil **0.23%**as a result there is a shortage of more than 99% of total requirement and hence demand for the patented product has not been met to an adequate extent;

(c) **Not available at a reasonably affordable price**- as described above, cost of importing one tablet of ONGLYZA in India is only about **Rs 0.80 /per tablet**. Whereas, same tablet is being sold in Indian market by BMS and AstraZeneca at a market price of about **Rs. 41-45/- per tablet**. Similarly cost of importing one tablet of KOMBIGLYZE in India only about **Rs. 0.92/ per tablet** but the same tablet is being sold in Indian market at a price of **Rs. 49/- per tablet**;

In a poor country like India where according to the recent reports of Rangarajan committee about 30% of the total population lives below poverty line which earns even **less than Rs. 32/- per day** in rural areas and **less than Rs. 47/- per day** in urban areas, the cost of one tablet of Patentee's medicine is even more than their whole day earning. Therefore, excessive high price of the medicines sold by Grantee/ Patentee in Indian market is a barrier to access of Saxagliptin for the poor patients of India. At this high price, the patented product Saxagliptin is not available to the general public at a reasonably affordable price. Thereby the reasonable requirement of public is not being met in terms of reasonably affordable price;

(d) on account of non-responsive to voluntary licence request as a strategy for non willingness to give voluntary licence, the establishment or development of commercial activities in India in respect of the patented product and supply thereof to needy diabetic patients is totally prejudiced;

(e) Invention not worked in India- even after passing a long period of about eight years from the date of grant (granted on April 30, 2007), the patentee has not taken adequate steps to manufacture Saxagliptin in India and make full use of the invention in India to an adequate extent that is reasonably practicable;

(f) the working of the patented product in the territory of India is hindered by the importation from abroad of the patented product by the patentee and those claiming under him;

13. The Applicant herein undertakes to submit certified copies of the Patent document IN206543 in due course of time and any other documents as may be required by The Patent Office.

14. THE TERMS AND CONDITIONS OF COMPULSORY LICENCE

After adjudication the learned Controller should decide to grant Compulsory Licence (CL) in favour of the Applicant herein (Lee Pharma Limited), wherein the Applicant is ready accept the same licence on the terms and conditions set out in the following points:

(I) **<u>Right to manufacture and sell</u>**:

the right to manufacture and sell Saxagliptin shall be limited to the territory of India. The Applicant shall not use the licence for sale to

other countries. Applicant shall take all necessary steps to ensure that the product is sold and available only within the territory of India.

(II) **Royalties:**

the Applicant agrees to pay the royalties to the Patentee at the rate as fixed by the Ld. Controller;

(III) **Price:**

the Applicant agrees to make available the patented product Saxagliptin to the public at the most possible reasonable and affordable price. In this regard, the Applicant proposes a price as follows:

- for Saxagliptin 2.5 mg and Saxagliptin 5 mg are as follows:

Product	Strength	Price/Strip of 14 Tablets (MRP in Rs.)	Price/Unit Tablet (MRP in Rs.)
Saxagliptin	2.5 mg	Rs. 378.00	Rs. 27.00
Saxagliptin	5 mg	Rs. 406.00	Rs. 29.00

- for Saxagliptin + Metformin (mg/mg) are as follows:

Product	Strength	Price/Strip of 7 Tablets (MRP in Rs.)	Price/Unit Tablet (MRP in Rs.)
Saxagliptin + Metformin XR	5/500 mg	Rs. 210.00	Rs. 30.00
Saxagliptin + Metformin XR	5/1000 mg	Rs. 220.50	Rs. 31.50

(IV) **Other terms by Controller:**

the Applicant agrees to be bound by any other terms and conditions as imposed by the Ld. Controller.

15. PRAYER

In view of the submissions and grounds presented in the preceding paragraphs, the Applicant humbly prays that; the Ld. Controller may be please to grant and issue Compulsory Licence (CL) in favour of the Applicant herein in respect of the Indian Patent No. 206543 based upon the terms and conditions the Ld. Controller may fit and proper.

Afzal Hasan
Afzal Hasan
of HASAN AND SINGH
IN/PA-1328
Advocate And Patent Agent
For LEE PHARMA LIMITED

Hyderabad
Date: June 25, 2015

VERIFICATION

Verified at Hyderabad on this 26th day of June, 2015 that the contents and statements made in above paragraphs are true to the best of knowledge, information and belief of the applicant. No part of it is false and nothing material has been concealed therefrom.

Afzal Hasan
Afzal Hasan
of HASAN AND SINGH
IN/PA-1328
Advocate And Patent Agent
For LEE PHARMA LIMITED

Hyderabad
Date: June 25, 2015

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Legal Status :	*Inforce*
Due date of next renewal	*05/03/2016*

Patent Number	206543	Date of Patent	05/Mar/2001
Application Number	IN/PCT/2002/01154/MUM	Date of Grant	30/Apr/2007
Type of Application	PCT NATIONAL PHASE APPLICATION	Date of Recordal	29/May/2007
Parent Application Number	---	Appropriate Office	MUMBAI
PCT International Application Number	PCT/US01/07151	PCT International Filing Date	05/Mar/2001

Grant Title :A CYCLOPROPYL-FUSED PYRROLIDINE-BASED COMPOUND

Serial No.	Name of Grantee	Grantee Address
1	BRISTOL-MYERS SQUIBB COMPANY	LAWRENCEVILLE-PRINCETON RD., P.O BOX 4000, PRINCETON, NEW JERSEY 08543-4000, UNITED STATES OF AMERICA.

Serial No.	Name of Pantentee	Address of Pantentee
1	ASTRAZENECA AB	SE-151 85, Sodertalje, Sweden.

Address of Service :REMFRY & SAGAR, Attorneys-at-Law, Gresham Assurance House, 1 Sir P.M.Road, MUMBAI 400 001,

Additional Address of Service : ---

Priority Date :N/A

Year:	Due dates for Renewal		CBR No:	CBR Date:	Renewal Amount:	Renewal Certificate No:	Date of Renewal:	Renewal Period:	
	Normal Due Date:	Due Date with Extension						From	To
3rd year	29/Aug/2007	29/Feb/2008	3952	03/Sep/2007	2000	3512	03/Sep/2007	05/Mar/2003	05/Mar/2004
4th year	29/Aug/2007	29/Feb/2008	3952	03/Sep/2007	2000	3512	03/Sep/2007	05/Mar/2004	05/Mar/2005
5th year	29/Aug/2007	29/Feb/2008	3952	03/Sep/2007	2000	3512	03/Sep/2007	05/Mar/2005	05/Mar/2006
6th year	29/Aug/2007	29/Feb/2008	3952	03/Sep/2007	2000	3512	03/Sep/2007	05/Mar/2006	05/Mar/2007
7th year	29/Aug/2007	29/Feb/2008	3952	03/Sep/2007	6000	3512	03/Sep/2007	05/Mar/2007	05/Mar/2008
8th year	05/Mar/2008	05/Sep/2008	1281	14/Feb/2008	6000	897	14/Feb/2008	05/Mar/2008	05/Mar/2009
9th year	05/Mar/2009	05/Sep/2009	1164	03/Feb/2009	6000	711	03/Feb/2009	05/Mar/2009	05/Mar/2010
10th year	05/Mar/2010	05/Sep/2010	2154	05/Feb/2010	6000	672	05/Feb/2010	05/Mar/2010	05/Mar/2011
11th year	05/Mar/2011	05/Sep/2011	1370	07/Feb/2011	12000	635	07/Feb/2011	05/Mar/2011	05/Mar/2012
12th year	05/Mar/2012	05/Sep/2012	1657	08/Feb/2012	12000	780	08/Feb/2012	05/Mar/2012	05/Mar/2013
13th year	05/Mar/2013	05/Sep/2013	1337	01/Feb/2013	12000	592	01/Feb/2013	05/Mar/2013	05/Mar/2014
14th year	05/Mar/2014	05/Sep/2014	1395	31/Jan/2014	12000	574	31/Jan/2014	05/Mar/2014	05/Mar/2015
15th year	05/Mar/2015	05/Sep/2015	18261	08/Dec/2014	24000	10101	08/Dec/2014	05/Mar/2015	05/Mar/2016
16th year	--	--	--	--	--	--	--	--	--
17th year	--	--	--	--	--	--	--	--	--
18th year	--	--	--	--	--	--	--	--	--
19th year	--	--	--	--	--	--	--	--	--
20th year	--	--	--	--	--	--	--	--	--

Serial No	Date of Entry	Particulars/Remarks
1	19/Aug/2014	"In pursuance of an application received on the 03.04.2014, made by ASTRAZENECA AB, of SE-151 85, Sodertalje, Sweden. Registered proprietors by virtue of Deed of Assignment dated 21.02.2014 and executed between

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		ASTRAZENECA AB as the one part and BRISTOL-MYERS SQUIBB COMPANY as the other part".

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206543 28
30.04.2007

FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS RULES, 2003
COMPLETE SPECIFICATION

[See Section 10; rule 13]

"A CYCLOPROPYL-FUSED PYRROLIDINE-BASED COMPOUND"

BRISTOL-MYERS SQUIBB COMPANY, a Delaware corporation of Lawrenceville-Princeton Rd., P.O Box 4000, Princeton, New Jersey 08543-4000, United States of America,

The following specification particularly describes the invention and the manner in which it is to be performed:

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Original
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25/08/2002

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The present invention relates to a cyclopropyl-fused pyrrolidine-based compound.

The present invention relates to cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV (DP-4), and to a method for treating diabetes, especially Type II diabetes, as well as hyperglycemia, Syndrome X, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as various immunomodulatory diseases and chronic inflammatory bowel disease, employing such cyclopropyl-fused pyrrolidines alone or in combination with another type antidiabetic agent and/or other type therapeutic agent.

Depeptidyl peptidase IV (DP-4) is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1(7-36), glucagon) in vivo and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) in vitro.

GLP-1(7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine. GLP-1(7-36) has multiple actions in vivo including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying. Based on its physiological profile, the actions of GLP-1(7-36) are expected to be beneficial in the prevention and treatment of type II diabetes and potentially obesity. To support

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this claim, exogenous administration of GLP-1(7-36) (continuous infusion) in diabetic patients has demonstrated efficacy in this patient population. Unfortunately GLP-1(7-36) is degraded rapidly in vivo and has been shown to have a short half-life in vivo (t1/2≈1.5 min). Based on a study of genetically bred DP-4 KO mice and on in vivo/in vitro studies with selective DP-4 inhibitors, DP-4 has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo. GLP-1(7-36) is degraded by DP-4 efficiently to GLP-1(9-36), which has been speculated to act as a physiological antagonist to GLP-1(7-36). Thus, inhibition of DP-4 in vivo should potentiate endogenous levels of GLP-1(7-36) and attenuate formation of its antagonist GLP-1(9-36) and thus serve to ameliorate the diabetic condition.

In accordance with the present invention, cyclopropyl-fused pyrrolidine-based compounds are provided which inhibit DP-4 and have the structure

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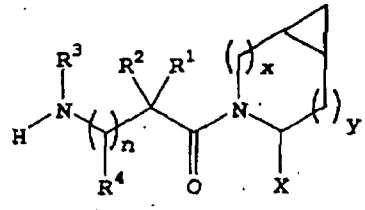

wherein x is 0 or 1 and y is 0 or 1 (provided that

x = 1 when y = 0 and

x = 0 when y = 1);

n is 0 or 1;

X is H or CN (that is cyano);

R^1, R^2, R^3 and R^4 are the same or different and are independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl,

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arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl and cycloheteroalkylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

and R^1 and R^3 may optionally be taken together to form $-(CR^5R^6)_m-$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, halo, amino, substituted amino, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R^4 may optionally be taken together to form $-(CR^7R^8)_p-$ where p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, halo, amino, substituted amino, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino,

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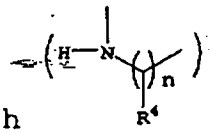
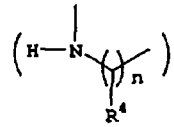
alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together



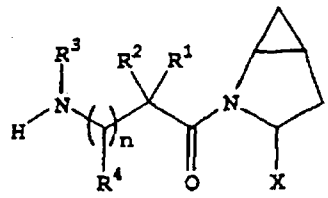
with R^4 form a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2;

or optionally R^1 and R^3 together with  form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

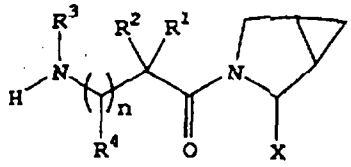
and including pharmaceutically acceptable salts thereof, and prodrug esters thereof, and all stereoisomers thereof.

Thus, the compounds of formula I of the invention include the following structures

IA



IB



In addition, in accordance with the present invention, a method is provided for treating diabetes, especially Type II diabetes, as well as impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases (such as scleroderma and

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multiple sclerosis), various immunomodulatory diseases (such as lupus erythematosis or psoriasis), AIDS, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease), inflammatory bowel syndrome, chemotherapy-induced intestinal mucosal atrophy or injury, anorexia nervosa, osteoporosis, Syndrome X, dysmetabolic syndrome, diabetic complications, hyperinsulinemia, obesity, atherosclerosis and related diseases, as well as inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), wherein a therapeutically effective amount of a compound of structure I (which inhibits DP 4) is administered to a human patient in need of treatment.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-734 (1997).

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter as well as any of the other disease states mentioned above, wherein a therapeutically effective amount of a combination of a compound of structure I and one, two, three or more of other types of antidiabetic agent(s) (which may be employed to treat diabetes and related diseases) and/or one, two or three or more other types of therapeutic agent(s) is administered to a human patient in need of treatment.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications, dysmetabolic syndrome, and hyperinsulinemia.

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

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The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than DP4 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-modulating agents (including anti-atherosclerosis agents), and/or one or more infertility agents, one or more agents for treating polycystic ovary syndrome, one or more agents for treating growth disorders, one or more agents for treating frailty, one or more agents for treating arthritis, one or more agents for preventing allograft rejection in transplantation, one or more agents for treating autoimmune diseases, one or more anti-AIDS agents, one or more anti-osteoporosis agents, one or more agents for treating immunomodulatory diseases, one or more agents for treating chronic inflammatory bowel disease or syndrome and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

In the above methods of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent or other type therapeutic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 500:1, preferably from about 0.1:1 to about 100:1, more preferably from about 0.2:1 to about 10:1.

Preferred are compounds of formula I wherein R^3 is H or alkyl, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxytricycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, or hydroxyalkylcycloalkyl, R^2 is H or alkyl, n is 0, X is CN, x is 0 or 1 and y is 0 or 1.

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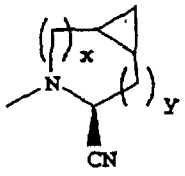
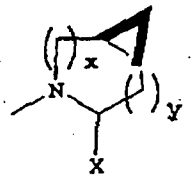
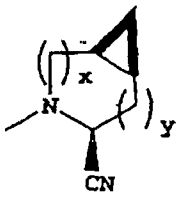
Most preferred are preferred compounds of formula I as described above where X is  or  and/or wherein the fused cyclopropyl group is identified as 

Thus, preferred compounds of formula I of the invention will include the moiety:

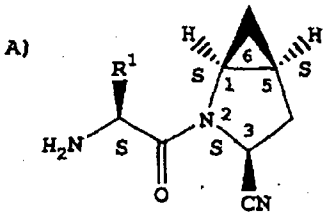




or



Particularly preferred are the following compounds:

A) 

[1S,2(2S),3S,5S]

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl or hydroxytricycloalkyl;

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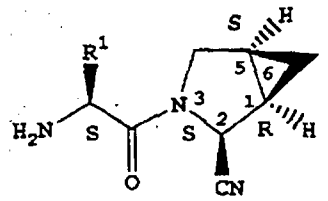
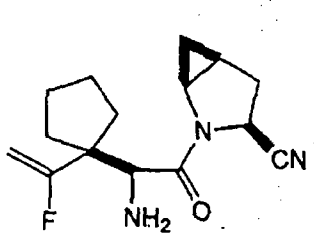
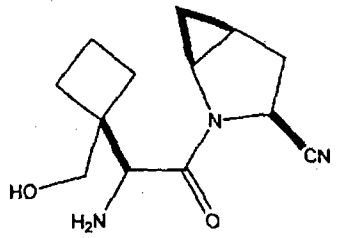
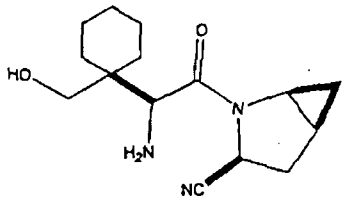
B) 

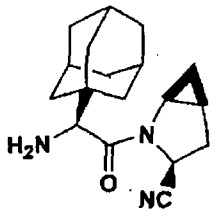
[1R,2S,3(2S),5S]

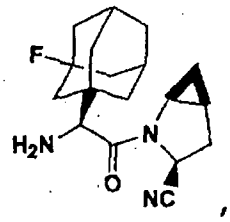
wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl or hydroxyalkylcycloalkyl as well as the following:

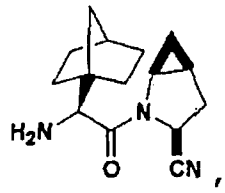


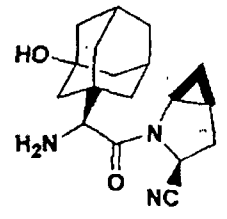




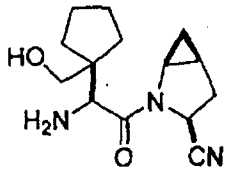




, 

, 

and



.

Compounds of the structure I may be generated by the methods as shown in the following reaction schemes and the description thereof.

Referring to Reaction Scheme 1, compound 1, where PG_1 is a common amine protecting group such as Boc, Cbz, or FMOC and X^1 is H or CO_2R^9 as set out below, may be generated by methods as described herein or in the literature (for example see Sagnard et al, Tet-Lett., 1995, 36, pp. 3148-3152, Tverezovsky et al, Tetrahedron,

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1997, 53, pp. 14773-14792, Hanessian et al, Bioorg. Med. Chem. Lett., 1998, 8, p. 2123-2128). Removal of the PG_1 group by conventional methods (e.g. (1) TFA or HCl when PG_1 is Boc, or (2) H_2/Pd/C, TMSI when PG_1 is Cbz, or (3) Et_2NH when PG_1 is (FMOC) affords the free amine 2. Amine 2 may be coupled to various protected amino acids such as 3 (where PG_2 can be any of the PG_1 protecting groups) using standard peptide coupling conditions (e.g. EDAC/HOAT, i-BuCOCOCl/TEA, PyBop/NMM) to afford the corresponding dipeptide 4. Removal of the amine protecting group PG_2 provides compound Ia of the invention where X=H.

In the case where $X^1=CO_2R^9$ (where R^9 is alkyl or aralkyl groups such as methyl, ethyl, t-butyl, or benzyl), the ester may be hydrolyzed under a variety of conditions, for example with aqueous NaOH in a suitable solvent such as methanol, THF, or dioxane, to provide the acid 5. Conversion of the acid group to the primary carboxamide, affording 6, may be effected by activation of the acid group (e.g. employing i-BuOCOCl/TEA or EDAC) followed by treatment with NH_3 or an ammonia equivalent in a solvent such as dioxane, ether, or methanol. The amide functionality may be converted to the nitrile group by a variety of standard conditions (e.g. $POCl_3$/pyridine/imidazole or cyanuric chloride/DMF or trifluoroacetic anhydride, THF, pyridine) to give 7. Finally, removal of the PG_2 protecting group similar to above provides compound of the invention Ib.

In a different sequence (Scheme 2), compound 1 where X^1 is CO_2R^9 may be saponified to the acid and subsequently amidated as described above to give amide 8. Removal of the PG_1 group followed by peptide coupling to 3 affords compound 6, an intermediate in the synthesis of Ib.

Alternately, the carboxamide group in 8 may be converted to the nitrile as described above to give compound 9. Deprotection of PG_1 affords 10 which may be

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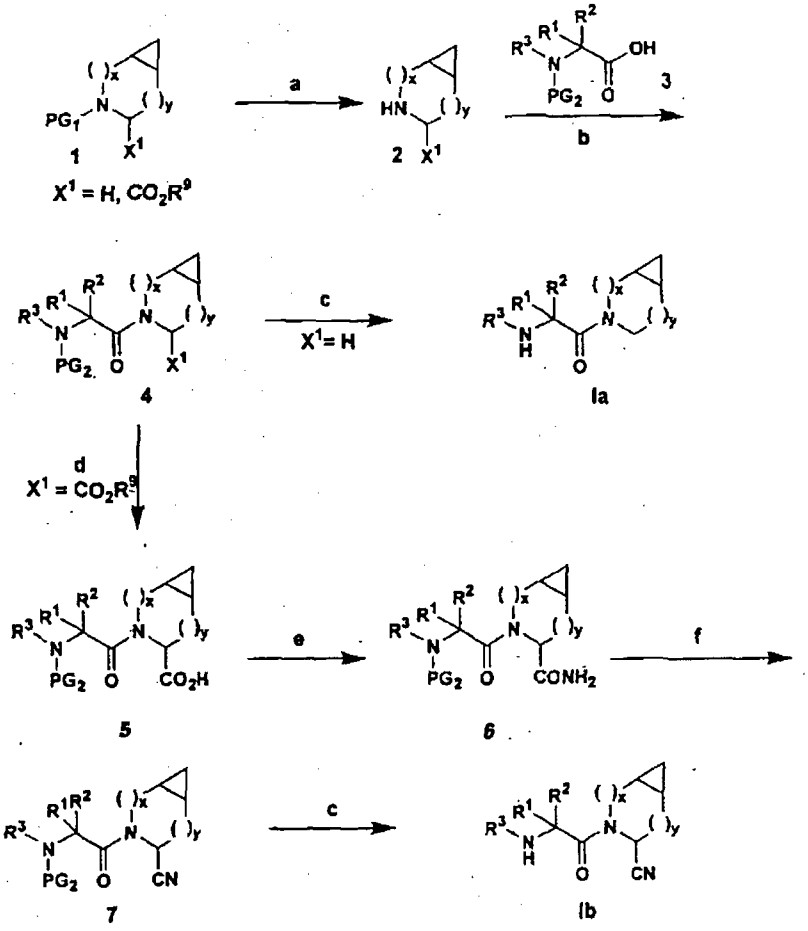
subject to standard peptide coupling conditions to afford 7, an intermediate in the synthesis of Ib. Compound 10 may also be generated by oxidation of the amine 2 (e.g. NCS) followed by hydrolysis and subsequent cyanide treatment. Compound 10 may be obtained as a mixture of stereoisomers or a single isomer/diastereomer which may be epimerized (employing conventional procedures) to afford a mixture of stereoisomers.

Scheme 1



a. PG_1 =Boc, TFA or HCl; PG_1 = Cbz, H_2/Pd/C or TMSI; PG_1 = FMOC, Et_2NH b. EDAC, HOBT, DMF or i-BuOCOCl/ TEA or PyBop, NMM c. PG_2 = PG_1, (see conditions for a) d. LiOH or NaOH MeOH or THF/H_2O *or dioxane e. i-BuOCOCl/ NMM or i-BuOCOCl/TEA or EDAC, then* NH_3 in dioxane or Et_2O f. $POCl_3$, pyridine, imidazole or cyanuric chloride, DMF or TFAA, THF, pyridine.

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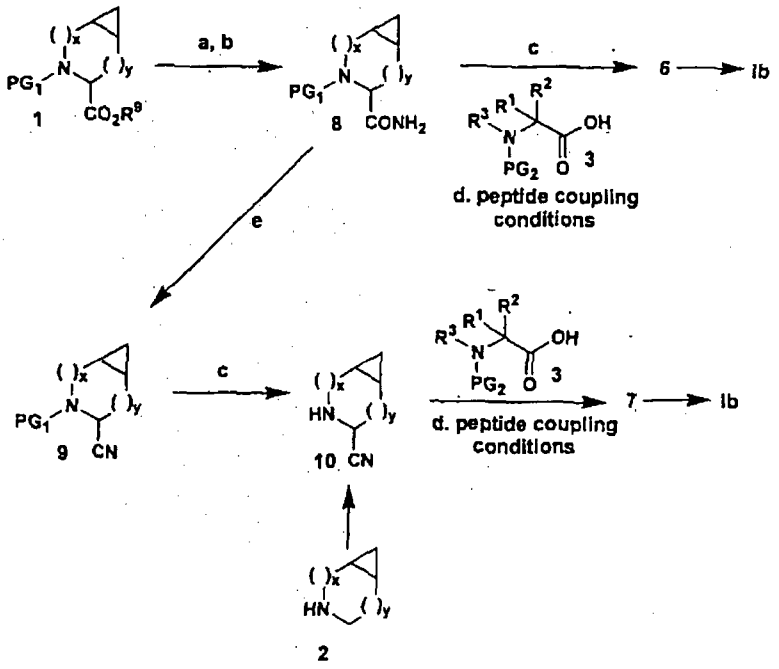
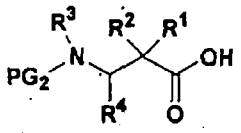
Scheme 2



a. LiOH or NaOH in MeOH or THF/H_2O or dioxane b. i-BuOCOCl/ NMM or i-BuOCOCl/TEA or EDAC, then NH_3 in dioxane or Et_2O c.PG_1 =Boc, TFA or HCl; PG_1 = Cbz, H_2/Pd/C or TMSI; PG_1 = FMOC, Et_2NH d. EDAC, HOBT, DMF or i-BuOCOCl/ TEA or PyBop, NMM e. $POCl_3$, pyridine, imidazole or cyanuric chloride, DMF.

In a like manner, β-amino acids such as



may be coupled with 2, the free amine of 8, or 10 to give the corresponding amides which may be converted to the β-amino acid derivatives of compound Ia or Ib following the same chemistry.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl,

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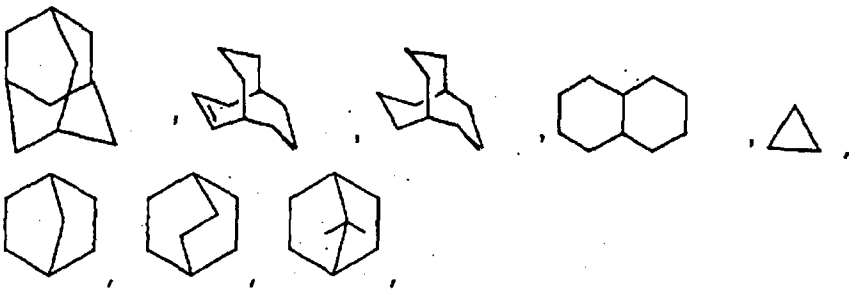
the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, alkylthio, arylalkylthio, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl) and tricyclic alkyl (tricycloalkyl), containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl, adamantyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, hydroxyalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.

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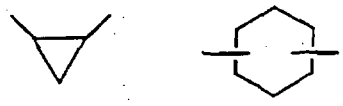
The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "cycloalkylene" as employed herein refers to a "cycloalkyl" group which includes free bonds and thus is a linking group such as



and the like, and may optionally be substituted as defined above for "cycloalkyl".

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain

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radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

The terms "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

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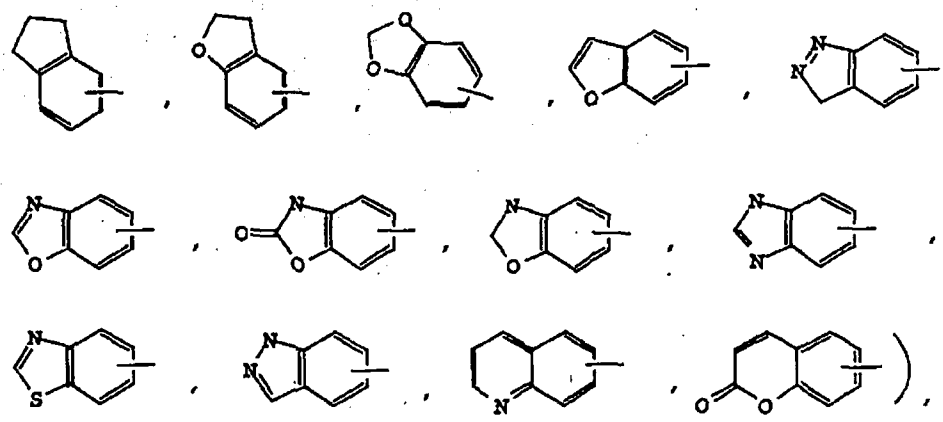
Unless otherwise indicated, the term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl,

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arylsulfonylamino or arylsulfon-aminocarbonyl and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with any of the R^1 groups or substituents for R^1 as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Unless otherwise indicated, the term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as

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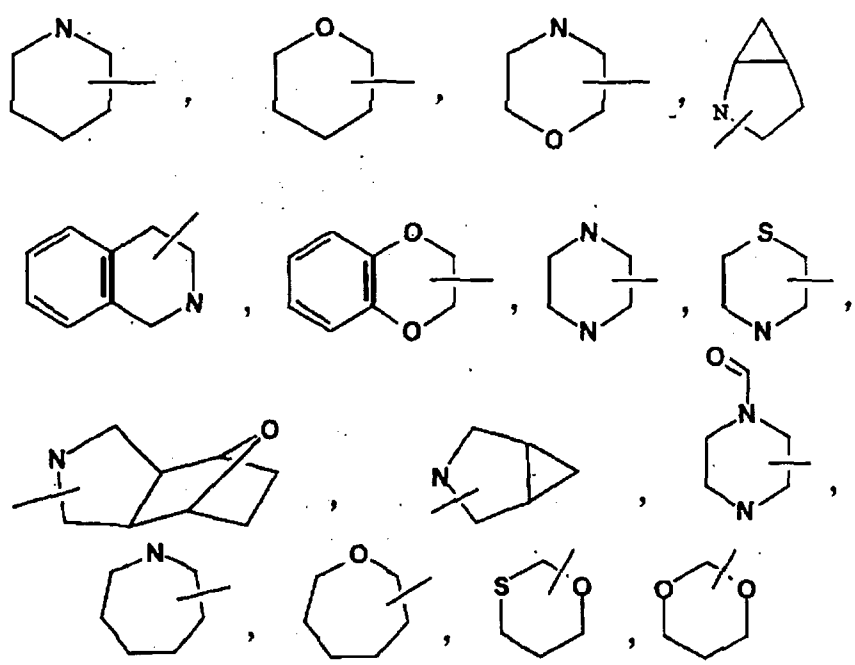
defined herein, refers to an organic radical linked to a carbonyl (C=O) group; examples of acyl groups include any of the R^1 groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_r$ (where r is 1, 2 or 3), such as:



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of the alkyl substituents set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2,

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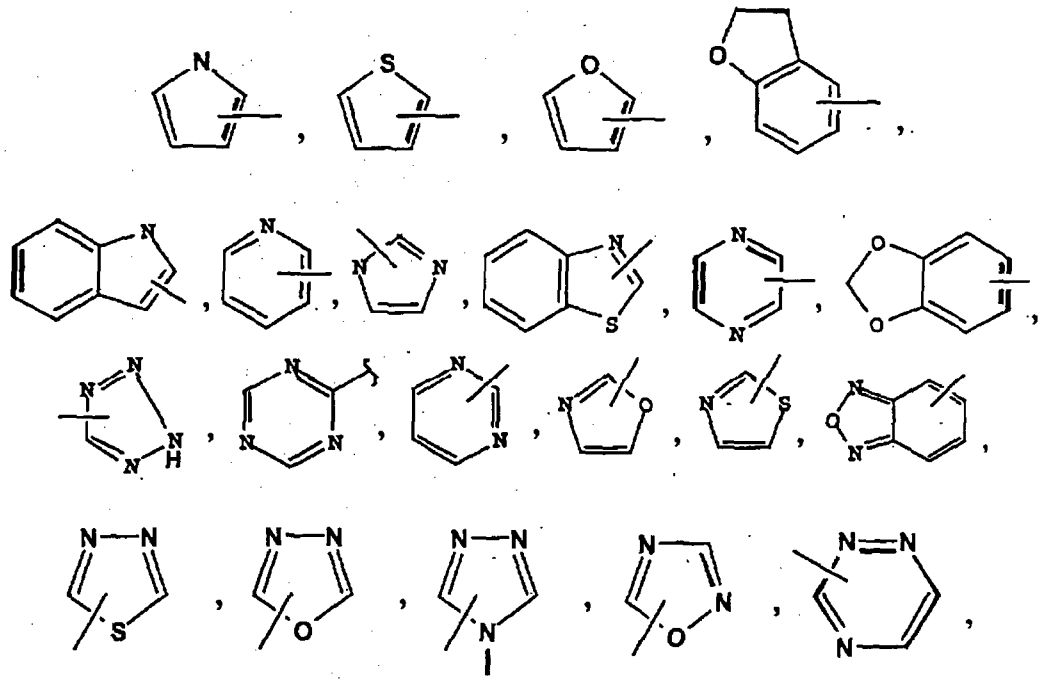
3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the substituents set out above for alkyl. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_r$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_r-$ chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

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The term "polyhaloalkoxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Where desired, the compounds of structure I may be used in combination with one or more other types of antidiabetic agents (employed to treat diabetes and related diseases) and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The other type of antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from DP4 inhibition and may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, SGLT2 inhibitors, PPAR α/γ dual agonists, aP2 inhibitors, glycogen phosphorylase inhibitors, advanced glycosylation end (AGE) products inhibitors, and/or meglitinides, as well as insulin,

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and/or glucagon-like peptide-1 (GLP-1) or mimetics thereof.

It is believed that the use of the compounds of structure I in combination with 1, 2, 3 or more other antidiabetic agents produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the other antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the

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range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 50:1.

The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in *NIDDM* patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda) Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, disclosure of which is incorporated herein by reference), or a GLP-1 mimic such as AC2993 or Exendin-4 (Amylin) and LY-315902 or LY-307167 (Lilly) and NN2211 (Novo-Nordisk), which may be administered via injection, intranasal, or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase

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inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration (for example inhalation spray) or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. application Serial No. 09/664,598, filed September 18, 2000, (attorney file LA29NP) the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

The other antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. application Serial No. 09/679,027, filed October 4, 2000 (attorney file

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LA49NP), which is incorporated herein by reference, employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and U.S. application Serial No. 09/519,079, filed March 6, 2000 (attorney file LA27NP), which is incorporated herein by reference, employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent which may be optionally employed in combination with the DP4 inhibitor of formula I may be a glycogen phosphorylase inhibitor such as disclosed in WO 96/39384, WO 96/39385, EP 978279, WO 2000/47206, WO 99/43663, and U.S. Patent Nos. 5,952,322 and 5,998,463, WO 99/26659 and EP 1041068.

The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The DP4 inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, SGLT2 inhibitor, aP2 inhibitor, or glycogen phosphorylase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 10:1.

The hypolipidemic agent or lipid-modulating agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, ATP

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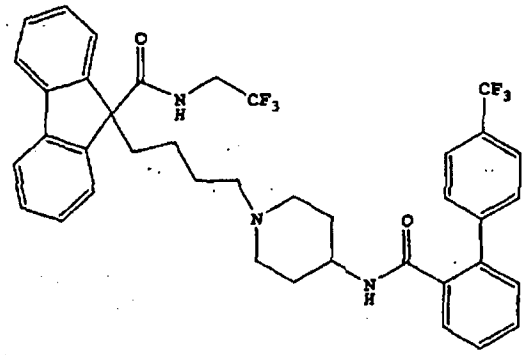
citrate lyase inhibitors, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246 as well as implitapide (Bayer).

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl] butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in

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U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, atavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate,

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bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98,

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Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

The lipid-modulating agent may be a cholesteryl ester transfer protein (CETP) inhibitor such as Pfizer's CP 529,414 (WO/0038722 and EP 818448) and Pharmacia's SC-744 and SC-795.

The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

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The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

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A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

The other type of therapeutic agent which may be optionally employed with the DP4 inhibitor of formula I

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may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug, an anorectic agent and/or a fatty acid oxidation upregulator.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopoamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor beta compound which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio) and GB98/284425 (KaroBio), with compounds of the KaroBio applications being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The fatty acid oxidation upregulator which may be optionally employed in combination with the compound of formula I can be famoxin (Genset).

The various anti-obesity agents described above may be employed in the same dosage form with the compound of

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formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

The infertility agent which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of clomiphene citrate (Clomid®, Aventis), bromocriptine mesylate (Parlodel®, Novartis), LHRH analogs, Lupron (TAP Pharm.), danazol, Danocrine (Sanofi), progestogens or glucocorticoids, which may be employed in amounts specified in the PDR.

The agent for polycystic ovary syndrome which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of gonadotropin releasing hormone (GnRH), leuprolide (Lupron®), Clomid®, Parlodel®, oral contraceptives or insulin sensitizers such as PPAR agonists, or other conventional agents for such use which may be employed in amounts specified in the PDR.

The agent for treating growth disorders and/or frailty which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of a growth hormone or growth hormone secretagogue such as MK-677 (Merck), CP-424,391 (Pfizer), and compounds disclosed in U.S. Serial No. 09/506,749 filed February 18, 2000 (attorney docket LA26), as well as selective androgen receptor modulators (SARMs), which is incorporated herein by reference, which may be employed in amounts specified in the PDR, where applicable.

The agent for treating arthritis which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of aspirin, indomethacin, ibuprofen, diclofenac sodium, naproxen, nabumetone (Relafen®, SmithKline Beecham), tolmetin sodium (Tolectin®, Ortho-McNeil), piroxicam (Feldene®, Pfizer), ketorolac tromethamine (Toradol®, Roche), celecoxib (Celebrex®, Searle), rofecoxib (Vioxx®, Merck) and the like, which may be employed in amounts specified in the PDR.

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Conventional agents for preventing allograft rejection in transplantation such as cyclosporin, Sandimmune (Novartis), azathioprine, Immuran (Faro) or methotrexate may be optionally employed in combination with the DP4 inhibitor of the invention, which may be employed in amounts specified in the PDR.

Conventional agents for treating autoimmune diseases such as multiple sclerosis and immunomodulatory diseases such as lupus erythematosis, psoriasis, for example, azathioprine, Immuran, cyclophosphamide, NSAIDS such as ibuprofen, cox 2 inhibitors such as Vioxx and Celebrex, glucocorticoids and hydroxychloroquine, may be optionally employed in combination with the DP4 inhibitor of the invention, which may be employed in amounts specified in the PDR.

The AIDS agent which may be optionally employed in combination with the DP4 inhibitor of the invention may be a non-nucleoside reverse transcriptase inhibitor, a nucleoside reverse transcriptase inhibitor, a protease inhibitor and/or an AIDS adjunct anti-infective and may be 1, 2, or more of dronabinol (Marinol®, Roxane Labs), didanosine (Videx®, Bristol-Myers Squibb), megestrol acetate (Megace®, Bristol-Myers Squibb), stavudine (Zerit®, Bristol-Myers Squibb), delavirdine mesylate (Rescriptor®, Pharmacia), lamivudine/zidovudine (Combivir™, Glaxo), lamivudine (Epivir™, Glaxo), zalcitabine (Hivid®, Roche), zidovudine (Retrovir®, Glaxo), indinavir sulfate (Crixivan®, Merck), saquinavir (Fortovase™, Roche), saquinovir mesylate (Invirase®, Roche), ritonavir (Norvir®, Abbott), nelfinavir (Viracept®, Agouron).

The above anti-AIDS agents may be employed in amounts specified in the PDR.

The agent for treating inflammatory bowel disease or syndrome which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of sulfasalazine, salicylates,

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mesalamine (Asacol®, P&G) or Zelmac®, (Bristol-Myers Squibb), which may be employed in amounts specified in the PDR or otherwise known in the art.

The agent for treating osteoporosis which may be optionally employed in combination with the DP4 inhibitor of the invention may be 1, 2, or more of alendronate sodium (Fosamax®, Merck, tiludronate (Skelid®, Sanofi), etidronate disodium (Didronel®, P&G), raloxifene HCl (Evista®, Lilly), which may be employed in amounts specified in the PDR.

In carrying our the method of the invention, a pharmaceutical composition will be employed containing the compounds of structure I, with or without another antidiabetic agent and/or other type therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 10 and 1,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of

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physiological saline, to produce an injectable preparation.

DP4 inhibitor activity of the compounds of the invention may be determined by use of an *in vitro* assay system which measures the potentiation of inhibition of DP4. Inhibition constants (Ki values) for the DP4 inhibitors of the invention may be determined by the method described below.

Purification of Porcine Dipeptidyl Peptidase IV

Porcine enzyme was purified as previously described (1), with several modifications. Kidneys from 15-20 animals were obtained, and the cortex was dissected away and frozen at -80°C. Frozen tissue (2000 -2500 g) was homogenized in 12 L of 0.25 M sucrose in a Waring blender. The homogenate then was left at 37°C for 18 hours to facilitate cleavage of DP-4 from cell membranes. After the cleavage step, the homogenate was clarified by centrifugation at 7000 X g for 20 min at 4°C, and the supernatant was collected. Solid ammonium sulfate was added to 60% saturation, and the precipitate was collected by centrifugation at 10,000 X g and was discarded. Additional ammonium sulfate was added to the supernatant to 80% saturation, and the 80% pellet was collected and dissolved in 20 mM Na_2HPO_4, pH 7.4.

After dialysis against 20 mM Na_2HPO_4, pH 7.4, the preparation was clarified by centrifugation at 10,000 X g. The clarified preparation then was applied to 300 mL of ConA Sepharose that had been equilibrated in the same buffer. After washing with buffer to a constant A_{280} the column was eluted with 5% (w/v) methyl α-D-mannopyranoside. Active fractions were pooled, concentrated, and dialyzed against 5 mM sodium acetate, pH 5.0. Dialyzed material then was flowed through a 100 mL Pharmacia Resource S column equilibrated in the same buffer. The flow through material was collected and contained most of the enzyme activity. Active material

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again was concentrated and dialyzed into 20 mM Na_2HPO_4, pH 7.4. Lastly, the concentrated enzyme was chromatographed on a Pharmacia S-200 gel filtration column to removed low molecular weight contaminants. Purity of column fractions was analyzed by reducing SDS-PAGE, and the purest fractions were pooled and concentrated. Purified enzyme was stored in 20% glycerol at -80°C.

Assay of Porcine Dipeptidyl Peptidase IV

Enzyme was assayed under steady-state conditions as previously described (2) with gly-pro-*p*-nitroanilide as substrate, with the following modifications. Reactions contained, in a final volume of 100 µl, 100 mM Aces, 52 mM TRIS, 52 mM ethanolamine, 500 µM gly-pro-*p*-nitroanilide, 0.2 % DMSO, and 4.5 nM enzyme at 25°C, pH 7.4. For single assays at 10 µM test compound, buffer, compound, and enzyme were added to wells of a 96 well microtiter plate, and were incubated at room temperature for 5 min. Reactions were started by addition of substrate. The continuous production of p-nitroaniline was measured at 405 nM for 15 min using a Molecular Devices Tmax plate reader, with a read every 9 seconds. The linear rate of *p*-nitroaniline production was obtained over the linear portion of each progress curve. A standard curve for p-nitroaniline absorbance was obtained at the beginning of each experiment, and enzyme catalyzed p-nitroaniline production was quantitated from the standard curve. Compounds giving greater than 50% inhibition were selected for further analysis.

For analysis of positive compounds, steady-state kinetic inhibition constants were determined as a function of both substrate and inhibitor concentration. Substrate saturation curves were obtained at gly-pro-*p*-nitroanilide concentrations from 60 µM to 3600 µM. Additional saturation curves also were obtained in the presence of inhibitor. Complete inhibition experiments contained 11 substrate and 7 inhibitor concentrations,

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with triplicate determinations across plates. For tight binding inhibitors with K_is less than 20 nM, the enzyme concentration was reduced to 0.5 nM and reaction times were increased to 120 min. Pooled datasets from the three plates were fitted to the appropriate equation for either competitive, noncompetitive or uncompetitive inhibition.

(1) Rahfeld, J. Schutkowski, M., Faust, J., *Neubert., Barth, A., and Heins, J. (1991) Biol. Chem.* Hoppe-Seyler, 372, 313-318.

(2) Nagatsu, T., Hino, M., Fuyamada, H., Hayakawa, T., Sakakibara, S., Nakagawa, Y., and Takemoto, T. (1976) Anal. Biochem., 74, 466-476.

The following abbreviations are employed in the Examples and elsewhere herein:

Ph = phenyl
Bn = benzyl
i-Bu = iso-butyl
Me = methyl
Et = ethyl
Pr = propyl
Bu = butyl
TMS = trimethylsilyl
FMOC = fluorenylmethoxycarbonyl
Boc or BOC = *tert*-butoxycarbonyl
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
HOAc or AcOH = acetic acid
DMF = N,N-dimethylformamide
EtOAc = ethyl acetate
THF = tetrahydrofuran
TFA = trifluoroacetic acid
Et_2NH = diethylamine
NMM = N-methyl morpholine

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n-BuLi = *n*-butyllithium
Pd/C = palladium on carbon
PtO_2 = platinum oxide
TEA = triethylamine
EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-[(3-(dimethyl)amino)propyl])-3-ethylcarbodiimide hydrochloride)
HOBT or HOBT•H_2O = 1-hydroxybenzotriazole hydrate
HOAT = 1-hydroxy-7-azabenzotriazole
PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate
min = minute(s)
h or hr = hour(s)
L = liter
mL = milliliter
µL = microliter
g = gram(s)
mg = milligram(s)
mol = mole(s)
mmol = millimole(s)
meq = milliequivalent
rt = room temperature
sat or sat'd = saturated
aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point

The following Examples represent preferred embodiments of the invention.

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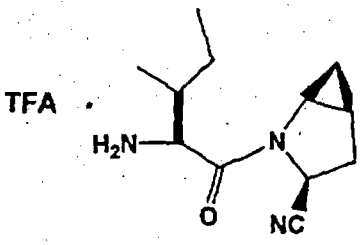
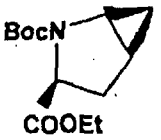
Example 1



Step 1.



Step 1 title compound was synthesized by following the literature procedure [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123-2128] *or* with the following modifications. L-pyroglutamic acid ethyl ester was N-protected as the t-butylcarbamate (Boc_2O, DMAP *or* NaH) and then dehydrated to the 4,5-dehydroproline ethyl ester in one pot by carbonyl reduction (triethylborohydride, toluene, -78°C) followed by dehydration (TFAA, lutidine). The title compound was obtained by cyclopropanation of the 4,5-dehydroproline ethyl ester (Et_2Zn, $ClCH_2I$, 1,2-dichloroethane, -15°C). A more detailed protocol is as follows:

Synthesis of 4,5-dehydro-L-proline ethyl ester: L-pyroglutamic acid ethyl ester (200 g, 1.27 mol) was dissolved in 1.2 liters of methylene chloride and treated sequentially with di-tert-butyldicarbonate (297 g, 1.36 mol) and a catalytic DMAP (1.55 g, 0.013 mol) at ambient temperature. After 6 h, the mixture was quenched with

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saturated brine and the organic phase was dried (Na_2SO_4) and filtered through a short silica gel column to give 323 g (100%) of N-Boc- L-pyroglutamic acid ethyl ester. N-Boc- L-pyroglutamic acid ethyl ester (160 g, 0.62 mol) was dissolved in 1 liter of toluene, cooled to -78°C and treated with lithium triethylborohydride (666 mL of a 1.0 M soln in THF) and added dropwise over 90 minutes. After 3 h, 2,6-lutidine (423 mL, 3.73 mol) was added dropwise followed by DMAP (0.2 g, 0.0016 mol). To this mixture was added TFAA (157 g, 0.74 mol) and the reaction was allowed to come to ambient temperature over 2 h. The mixture was diluted with EtOAc and water and the organics were washed with 3 N HCl, water, aqueous bicarbonate and brine and dried (Na_2SO_4) and filtered through a silica gel plug to give 165 g of the crude 4,5-dehydroproline ethyl ester that was purified by flash column chromatography on silica gel with 1:5 ethyl acetate:hexanes to give 120 g, 75% of the olefin.

Cyclopropanation of 4,5-dehydro-L-proline ethyl ester: 4,5-Dehydro-L-proline ethyl ester (35.0 g, 0.145 mol) was added to a solution of neat Et_2Zn (35.8 g, 0.209 mol) in 1 liter of 1,2-dichloroethane at -15°C. To this mixture was added a dropwise addition of $ClCH_2I$ (102 g, 0.58 mol) over 1 h and the mixture stirred at -15°C for 18 h. The reaction was quenched with saturated aqueous bicarbonate and the solvent was evaporated and the reaction was taken up in EtOAc, washed with brine and purified by silica gel chromatography using a stepwise gradient of from 20% EtOAc/hexanes to 50% EtOAc/hexanes to give 17.5 g (50%) of diastereomerically pure step 1 title compound.

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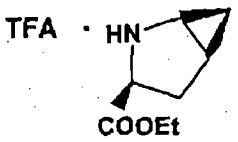
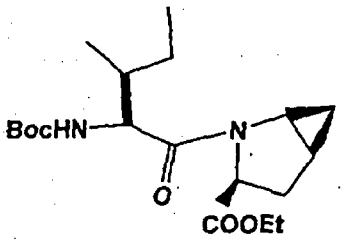
Step 2.



To a stirred solution of Step 1 compound (411 mg, 1.61 mmol) in CH_2Cl_2 (1.5 mL) at rt was added TFA (1.5 mL). The reaction mixture was stirred at rt for 2 h and evaporated. The residue was diluted with CH_2Cl_2 and then evaporated and re-evaporated three times to give the title compound as a colorless oil, 433 mg, 100% yield.

Step 3.



To a stirred solution of (*S*)-N-tert-butoxycarbonyl-isoleucine (372.6 mg, 1.61 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.25 g, 2.42 mmol) in CH_2Cl_2 (6 mL) under nitrogen at rt was added 4-methylmorpholine (NMM) (0.36 mL, 3.2 mmol). After 5 min, a solution of Step 2 compound (433 mg, 1.61 mmol) and NMM (0.27 mL, 2.4 mmol) in CH_2Cl_2 (1 mL) was added. After addition, the reaction mixture was stirred under nitrogen at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 4% $KHSO_4$ (10 mL), aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography (1:4 EtOAc/hexane) gave the title compound as a colorless oil, 530 mg, 89% yield.

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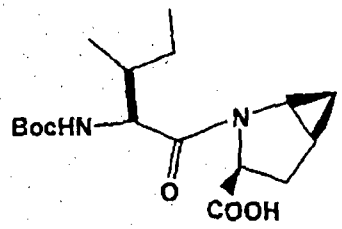
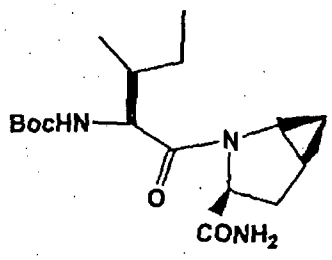
Step 4



To a stirred solution of Step 3 compound (530 mg, 1.44 mmol) in MeOH (4 mL) and H_2O (4 mL) at rt was added LiOH-H_2O (91 mg, 2.16 mmol). The reaction mixture was stirred at rt overnight and evaporated. Water (10 mL) was added to the residue and extracted with Et_2O (2 x 10 mL). The aqueous layer was acidified to ~pH 4 by adding 4% $KHSO_4$ dropwise. The milky solution was extracted with EtOAc (15 mL x 3). Combined EtOAc layers were washed with brine, dried over Na_2SO_4 and evaporated to give the title compound as a white solid, 440 mg, 90% yield.

Step 5



To a stirred solution of Step 4 compound (300 mg, 0.88 mmol) in THF (6 mL) at -15°C under nitrogen, was added 4-methylmorpholine (0.12 mL, 1.06 mmol) and then isobutyl chloroformate (0.13 mL, 0.97 mmol) over 2 min. White precipitate was formed. The reaction mixture was stirred at -15°C under nitrogen for 25 min and a solution of NH_3 in dioxane (8.8 mL, 4.4 mmol) was added. The reaction mixture was stirred at -15°C for 30 min, warmed to rt and stirred at rt overnight. The reaction mixture was quenched by 4% $KHSO_4$ to ~pH 4 and extracted with EtOAc (20 mL x 3). The extracts were combined, washed with brine

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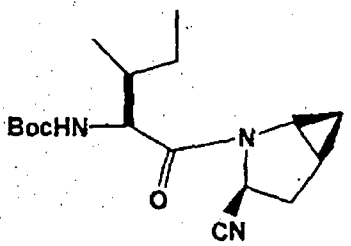
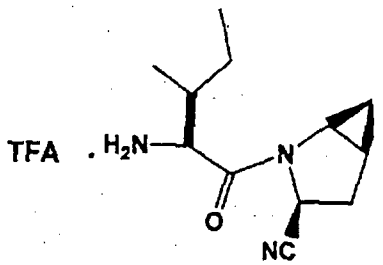
(10 mL) dried (Na_2SO_4) and evaporated. Purification by flash column chromatography (1:1 EtOAc/hexane) gave the title compound as a white foam, 268 mg, 90% yield.

Step 6



To a stirred solution of Step 5 compound (248 mg, 1.38 mmol) and imidazole (94 mg, 1.38 mmol) in dry pyridine (12 mL) at -35°C under nitrogen was added $POCl_3$ (0.26 mL, 2.76 mmol) dropwise. The reaction mixture was stirred between -35°C to -20°C for 1 h and evaporated. CH_2Cl_2 (10 mL) was added and white precipitates were formed. After filtration, the filtrate was concentrated and purified by flash chromatography (2:5 EtOAc/hexane) to give the title compound as a colorless oil, 196 mg, 88% yield.

Step 7



To a stirred solution of Step 6 compound (130 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) at rt was added TFA (2 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a pre-cooled slurry of $NaHCO_3$ (3.8 g) in H_2O (3 mL). The mixture was extracted with CH_2Cl_2 (6 mL x 5), and the combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compound as a white powder, 77 mg. 57% yield, mp =

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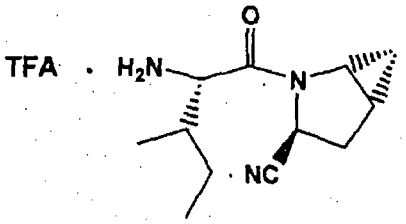
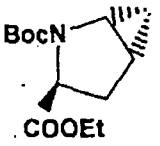
141-143°C. LC/MS gave the correct molecular ion [$(M+H)^+$ = 222] for the desired compound.

Example 2

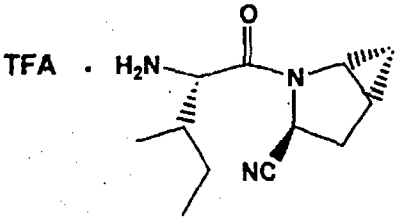


Step 1



Step 1 title compound was synthesized by following the literature procedure. [Stephen Hanessian, Ulrich Reinhold, Michel Saulnier, and Stephen Claridge; Bioorganic & Medicinal Chemistry Letters **8** (1998) 2123-2128.]

Step 2



The title compound was prepared from Step 1 compound, employing the same procedure as that described for *Example 1, Steps 2-6. LC/MS gave the correct molecular* ion [$(M+H)^+$ = 222] for the desired compound.

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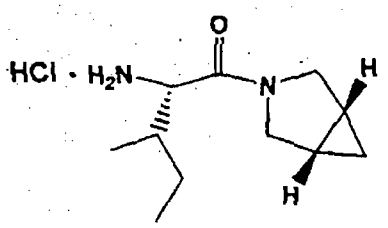
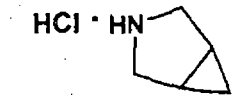
Example 3

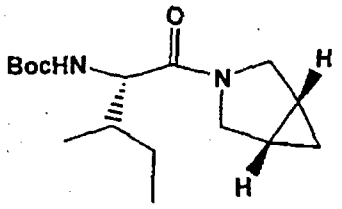


Step 1



Step 1 title compound was prepared by following the literature procedure. [Willy D. Kollmeyer, U.S. Patent 4,183,857.].

Step 2



To a stirred solution of (*S*)-N-tert-butoxycarbonyl-isoleucine (231 mg, 1 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (780 mg, 1.5 mmol) in CH_2Cl_2 (6 mL) under nitrogen at rt was added 4-methylmorpholine (0.33 mL, 3 mmol). After 5 min, Step 1 compound (120 mg, 1 mmol) was added in one portion. The reaction mixture was stirred under nitrogen at rt overnight and then diluted with CH_2Cl_2 (30 mL), washed with 4.1% $KHSO_4$ (10 mL), aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4 x 20 cm column, 1:3 EtOAc/hexane) gave the title compound as a colorless oil, 290 mg, 90% yield. LC/MS gave the correct molecular ion [$(M+H)^+$ = 297] for the desired compound.

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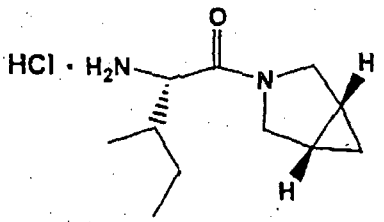
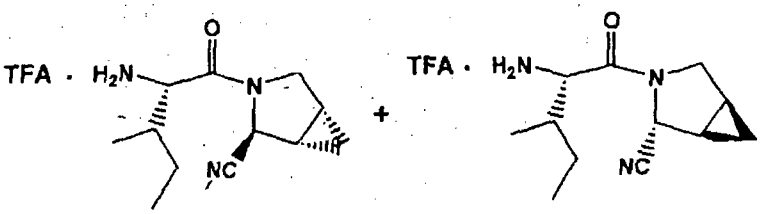
Step 3



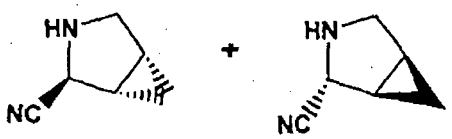
The reaction mixture of Step 2 compound (220 mg, 0.74 mmol) and 4 M HCl in dioxane (1.5 mL, 6 mmol) was stirred at rt for 2 h and evaporated under reduced pressure. Et_2O was added to the residue and a precipitate was formed. Et_2O was decanted and this was done three times. The precipitate was dried *in vacuo* to give the title compound as a white powder, 130 mg (76% yield), mp 205-206°C. LC/MS gave the correct molecular ion [$(M+H)^+$ = 197] for the desired compound.

Examples 4-4A



(Example 4) (Example 4A)

Step 1



Step 1 title compound, as a 1:1 ratio of enantiomers, was prepared by following the literature procedure. [Willy D. Kollmeyer, U.S. Patent 4,183,857.]

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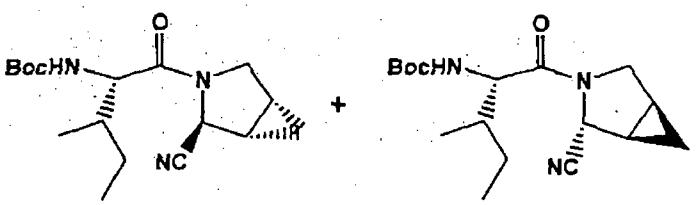
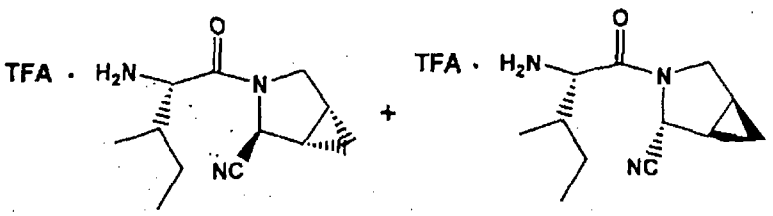
Step 2



A slurry of (*S*)-N-*tert*-butoxycarbonyl-isoleucine (92.5 mg, 0.4 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide(77 mg, 0.4 mmol) and HOAT (54.4 mg, 0.4 mmol) in $ClCH_2CH_2Cl$ (0.3 mL) was stirred under nitrogen at *rt for 1 h, then Step 1 compound (22 mg, 0.2 mmol) was* added, followed by Et_3N (0.015 mL, 0.1 mmol). The reaction mixture was stirred under nitrogen at rt overnight and then diluted with CH_2Cl_2 (3 mL), washed with H_2O (1 mL), aqueous $NaHCO_3$(1 mL) and brine (1 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4 x 12 cm column, 2:7 EtOAc/hexane) gave the title compound as a colorless oil, 33 mg, 51% yield. LC/MS gave the correct molecular ion [$(M+H)^+$ = 322] for the desired compound.

Step 3



(Example 4) (Example 4A)

To a stirred solution of Step 2 compound (30 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL) at rt was added TFA (0.5 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a precooled slurry of $NaHCO_3$ (0.8 g) in H_2O (1 mL). The mixture was extracted with CH_2Cl_2 (2 mL x 5), and combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compounds as a 1:1 ratio of

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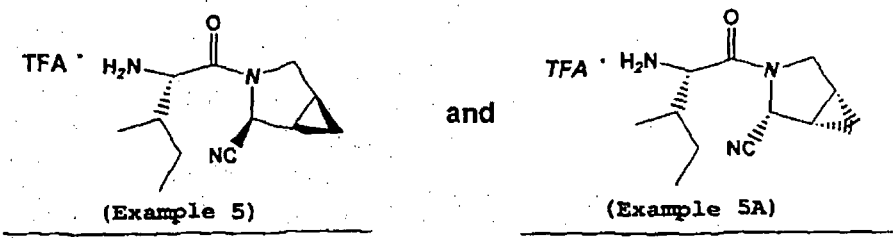
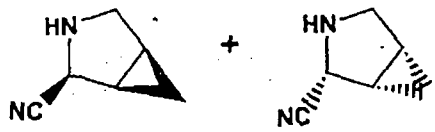
diastereomers, 22 mg, 73% yield. LC/MS gave the correct molecular ion [$(M+H)^+$ = 222] for the desired compounds.

Examples 5-5A



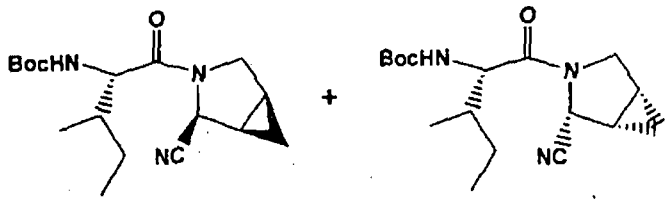
(Example 5) (Example 5A)

Step 1



To a solution of Example 4, Step 1 compound (150 mg, 1.39 mmol) in 2-propanol (0.8 mL), was added NaCN (40 mg, 1.0 mmol). The reaction mixture was heated to reflux for 3 h. After cooling to rt, the reaction mixture was evaporated and then slurried in Et_2O (5 mL). After filtration, the filtrate was evaporated to give Example 4 Step 1 compounds and Example 5 Step 1 compounds (140 mg, 93%) as a 2:1 mixture of diastereomers, each as a racemic mixture.

Step 2



A slurry of (S)-N-tert-butoxycarbonyl-isoleucine (595 mg, 2.57 mmol), 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide(493 mg, 2.57 mmol) and 1-hydroxy-7-azabenzotriazole (350 mg, 2.57 mmol) in $ClCH_2CH_2Cl$ (2 mL) was stirred under nitrogen at rt for 1 h, then Step 1 compound mixture (139 mg, 1.28 mmol) was added. The

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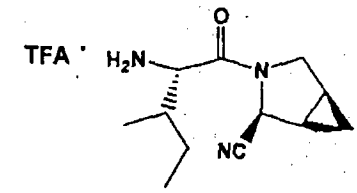
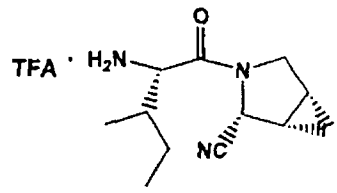
reaction mixture was stirred under nitrogen at rt overnight and then diluted with CH_2Cl_2 (30 mL), washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (2.4 x 20 cm column, 1:3 EtOAc/hexane) gave the Example 4, Step 2 compound (260 mg), and the title compounds (105 mg) as a ratio of 1:1 diastereomers. LC/MS gave the correct molecular ion [$(M+H)^+$ = 322] for the desired compounds.

Step 3



(Example 5)

and



(Example 5A)

To a stirred solution of Step 2 compounds (104 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) at rt was added TFA (1 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was added slowly to a precooled slurry of $NaHCO_3$ (2 g) in H_2O (2 mL). The mixture was extracted with CH_2Cl_2 (4 mL x 4), and combined CH_2Cl_2 layers were evaporated and purified by preparative HPLC to give the title compound Example 5 (36 mg) and Example 5A (36 mg). LC/MS gave the correct molecular ion [$(M+H)^+$ = 222] for the desired compounds.

Example 6

General Method A: Parallel array synthesis methods for preparation of inhibitors from commercially available amino acids. As shown in Scheme 3, the ester 11, described in Example 1 Step 1, was saponified to the acid with LiOH in THF/H_2O and converted to the amide 12 by treatment with isobutyl chloroformate/NMM followed by ammonia in dioxane. The Boc protecting group was removed under acidic conditions using TFA in methylene chloride to give **13**. The TFA salt was coupled to Boc-*t*-

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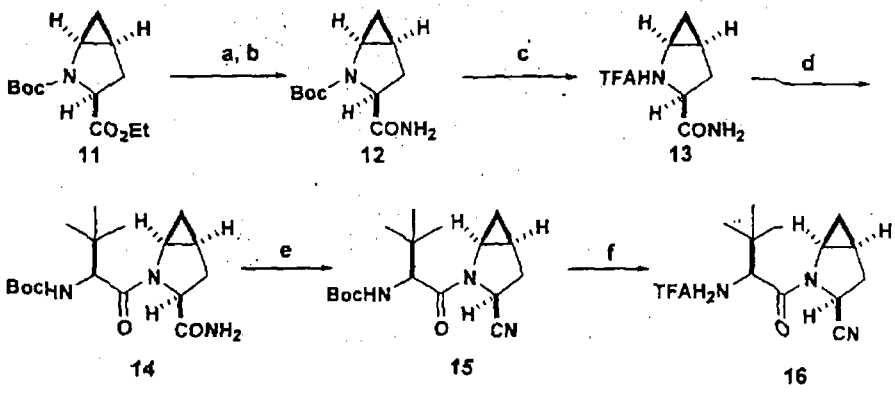
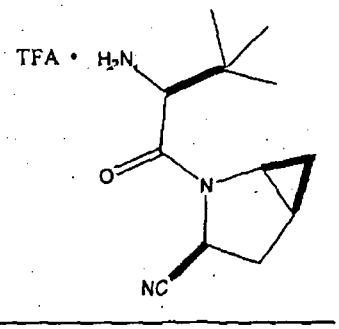
butylglycine using either EDAC/HOBT/DMF or EDAC/DMAP/CH_2Cl_2 to give **14**. The amide was dehydrated to the nitrile **15** using $POCl_3$/imidazole in pyridine at ~20°C and finally deprotected with TFA in CH_2Cl_2 at ambient temperature to afford the target **16**.

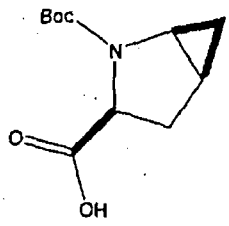
Scheme 3, General Method A (Examples 6-27)



a. LiOH inTHF/H_2O or MeOH/ H_2O b. i-BuOCOCl/ NMM or i-BuOCOCl/TEA at -30C or EDAC, then NH_3 in dioxane or Et_2O at RT c.TFA, CH_2Cl_2, RT d. Boc-t-butylglycine and PyBop/ NMM or EDAC, DMAP, CH_2Cl_2 e. $POCl_3$, pyridine, imidazole, -20C f. TFA, CH_2Cl_2, RT



Step 1



To a stirred solution of Example 1 Step 1 compound (1.40 g, 5.49 mmol) in 40 mL of a 1:1 methanol:water solution at rt was added lithium hydroxide (0.20 g, 8.30 mmol). The reaction mixture was stirred at rt for 18 h and then

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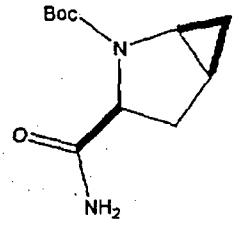
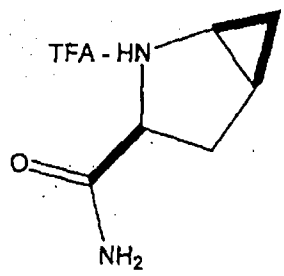
heated to 50°C for 2 h. The mixture was diluted with equal volumes of ether and water (50 mL) and then acidified with $KHSO_4$ to pH 3. The milky solution was extracted with ether (3 X 20 mL). The combined ether layers were dried over Na_2SO_4 and evaporated. The residue was stripped from toluene (2 X 10 mL) and dried under reduced pressure to give the title compound as a thick syrup, 1.20 g, 96%.

Step 2



To a stirred solution of Step 1 compound (1.20 g, 5.28 mmol) in THF (20 mL) at -15°C under nitrogen was added 4-methylmorpholine (0.71 mL, 6.50 mmol) and then isobutyl chloroformate (0.78 mL, 6.00 mmol) over 5 min. The reaction was stirred at -15°C for 30 min, cooled to -30°C and treated with a solution of NH_3 in dioxane (50 mL, 25 mmol). The reaction mixture was stirred at -30°C for 30 min, warmed to rt and stirred overnight. The reaction mixture was quenched with citric acid solution (pH 4) and extracted with ether (3 X 50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel with EtOAc gave the Step 2 compound, 1.00 g, 84%.

Step 3



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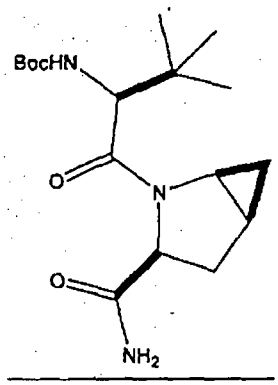
To a stirred solution of Step 2 compound (0.90 g, 4.00 mmol) in CH_2Cl_2 (3 mL) at 0°C was added TFA (3 mL). The reaction mixture was stirred at 0°C for 18 h. The reaction mixture was concentrated under reduced pressure to produce title compound in the form of a thick oil, 0.98 g, 100%. The oil gradually solidified upon prolonged standing.

Step 4



An oven-dried 15-mL test tube was charged with Step 3 compound (56 mg, 0.22 mmol), N-*tert*-butoxycarbonyl-(L)-*tert*-leucine (53 mg, 0.23 mmol), dimethylaminopyridine (0.11 g, 0.88 mmol), and CH_2Cl_2 (4 mL). The tube was sealed under nitrogen atmosphere and treated with 1-[(3-(dimethyl)amino)propyl]-3-ethylcarbodiimide (84 mg, 0.44 mmol). The mixture was placed in a shaker and vortexed overnight. The product was purified by solid phase extraction using a United Technology SCX column (2 g of sorbent in a 6 mL column) by loading the material on a SCX ion exchange column and successively washing with CH_2Cl_2 (5 mL), 30% methanol in CH_2Cl_2 (5 mL), 50% methanol in CH_2Cl_2 (5 mL) and methanol (10 mL). The product containing fractions were concentrated under reduced pressure to give the desired amide. Further purification by reverse phase preparative column chromatography on a YMC S5 ODS 20 X 250 mm column gave the title compound, 50 mg (68% yield). Purification conditions: Gradient elution from 30% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 15 min. 5 min. hold at 90%

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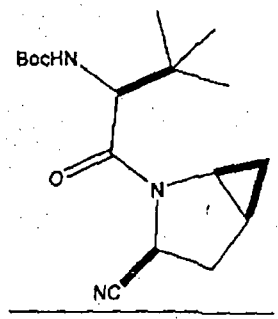
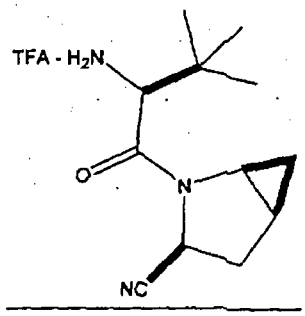
methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time: 14 min.

Step 5



An oven-dried 15-mL test tube was charged with Step 4 compound (50 mg, 0.15 mmol), imidazole (31 mg, 0.46 mmol), and pyridine (1 mL). The tube was sealed under nitrogen atmosphere and cooled to -30°C. Slow addition of $POCl_3$ (141 mg, 88 uL, 0.92 mmol) gave after mixing a thick slurry. The tube was mixed at -30°C for 3 h and the volatiles evaporated. The product was purified by solid phase extraction using a United Technology silica extraction column (2 g of sorbent in a 6 mL column) by loading the material on a silica column and successively washing with CH_2Cl_2 (5 mL), 5% methanol in CH_2Cl_2 (5 mL), 7% methanol in CH_2Cl_2 (5 mL) and 12% methanol in CH_2Cl_2 (10 mL). The product containing fractions were pooled and concentrated under reduced pressure to give the title compound, 46 mg, 96%.

Step 6



An oven-dried 15-mL test tube was charged with Step 5 compound (0.45 mg, 0.14 mmol), CH_2Cl_2 (1 mL), and TFA (1 mL). The reaction mixture was vortexed for 40 min at rt,

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diluted with toluene (4 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20 X 250 mm column to give the Example 6 compound, 14 mg, 35%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/0.1 TFA over 18 min; 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time: 10 min.

Examples 7-27 were prepared from amino acids available from commercial sources according to the procedure in Example 6.

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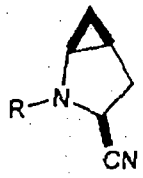
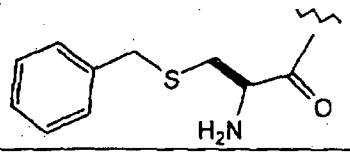
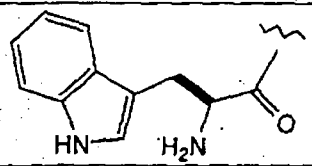
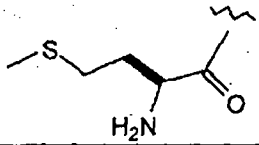
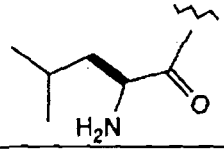
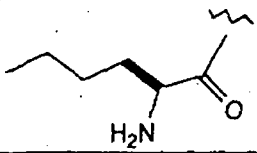
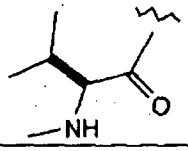
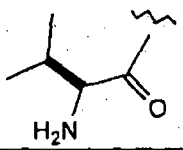
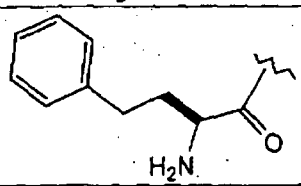
Table 1



Example	R	[M + H]
7		302
8		295
9		240
10		222
11		222
12		222
13		208
14		270

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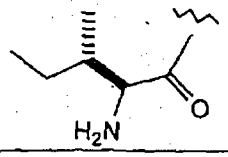
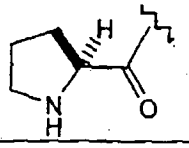
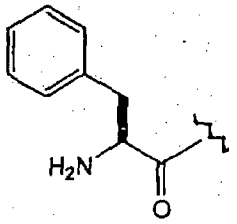
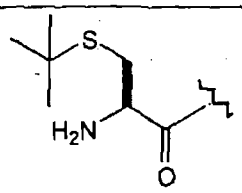
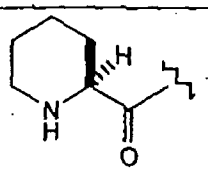
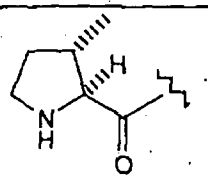
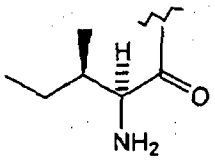
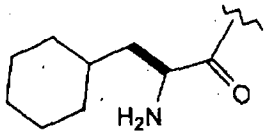
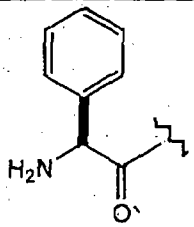
15		222
16		206
17		256
18		268
19		220
20		220
21		210
22		262
23		242

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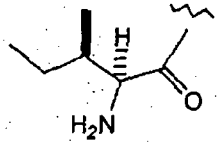
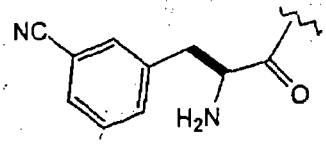
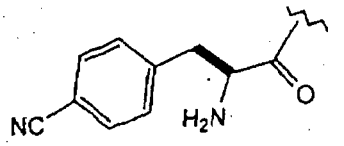
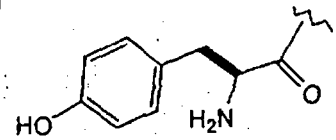
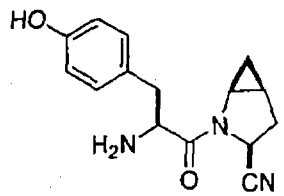
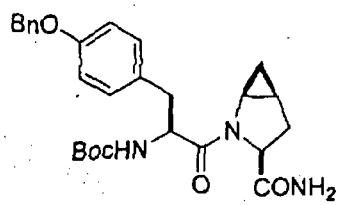
24		210
25		281
26		281
27		272

Example 27



Step 1



(2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt (53 mg, 0.22 mmol) was coupled to N-Boc-L-Tyrosine-benzyl ether(82 mg, 0.22 mmol) using PyBop (172 mg, 0.33 mmol) and N-methylmorpholine (67 mg, 0.66 mmol) in 4 mL CH_2Cl_2. The reaction stirred for 16 h, was taken up in EtOAc, washed with H_2O, 1N aqueous HCl, brine, then evaporated and purified by silica gel flash chromatography to give the coupled product (FAB MH+ 480).

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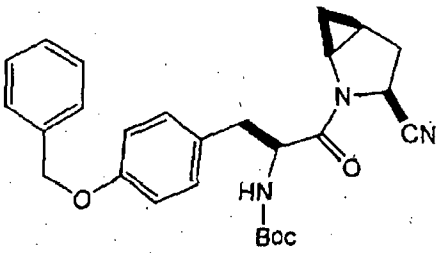
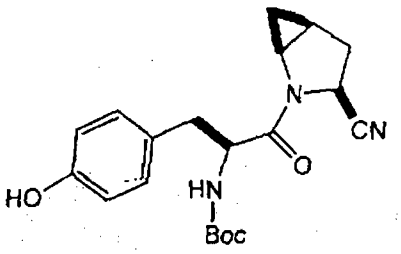
Step 2



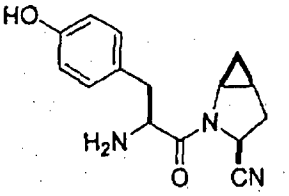
The Step 1 amide was dehydrated to the nitrile using the general method C (which follows Example 29) (FAB MH+ 462).

Step 3



The Step 2 benzyl ether was cleaved by catalytic hydrogenolysis using 10% palladium on carbon and 1 atmosphere hydrogen gas in MeOH at rt for 1.5 h. The reaction was filtered through celite and concentrated to an oil and taken on without further purification (FAB MH+ 372).

Step 4



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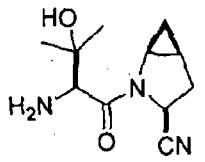
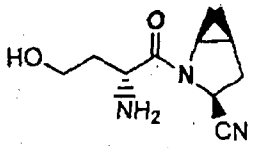
Step 3 N-[N-Boc-L-Tyrosine-]-(2S,4S,5S)-2-cyano-4,5-methano-L-prolylamide was dissolved in CH_2Cl_2 and TFA was added at rt. The reaction stirred for 1 h and was evaporated and purified by preparative HPLC as described in general method B (set out following Example 29) to afford the title compound (FAB MH+ 272).

Example 28

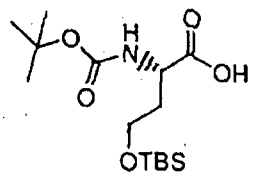


The title compound was prepared by coupling (2S,4S,5S)-4,5-methano-L-proline carboxylamide, TFA salt described in Example 6 Step 3 compound with N-(*tert*-butyloxy-carbonylhydroxyvaline. After hydroxyl protection with triethylsilyl chloride and dehydration of the amide with $POCl_3$/imidazole in pyridine and deprotection (N-terminal nitrogen and valine hydroxyl) with TFA using general method C (FAB MH+ 224), the title compound was obtained.

Example 29



Step 1



N-Boc-L-homoserine (1.20 g, 5.47 mmol) upon treatment with *tert*-butyldimethylsilyl chloride (1.67 g, 11.04

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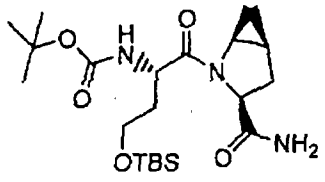
mmol) and imidazole (938 mg, 13.8 mmol) in THF (17 mL) was stirred as thick slurry for 48 h under N_2. The solvent was evaporated, and the crude material was dissolved in MeOH (10 mL). The resulting solution was stirred at rt for 2 h. The solvent was evaporated, and the crude material was diluted with CH_2Cl_2 (50 mL) and treated with 0.1N HCl (2x10 mL). The CH_2Cl_2 layer was washed with brine and dried over $MgSO_4$. Removal of the volatiles gave title compound as an oil (1.8 g), which was used without further purification (LC/Mass, + ion): 334 (M+H).

Step 2



To a stirred solution of Step 1 compound (333 mg, 1.0 mmol) in 6 mL of CH_2Cl_2 was added 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (256 mg, 1.32 mmol). The solution was then stirred at rt for 30 min, followed by addition with Example 6 Step 3 amine TFA salt (160 mg, 0.66 mmol) and 4-(dimethylamino)pyridine (244 mg, 2.0 mmol). The solution was then stirred at rt overnight. The mixture was diluted with CH_2Cl_2 (5 mL) and washed sequentially with H_2O, 10% citric acid, brine, then dried over Na_2SO_4 and evaporated to give the title compound (350 mg) which was used without further purification (LC/Mass, + ion): 442 (M+H).

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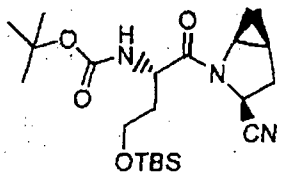
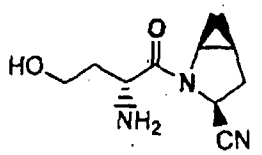
Step 3



An oven-dried 10-mL round bottomed flask was charged with Step 2 compound (350 mg, 0.79 mmol), imidazole (108 mg, 1.58 mmol), pyridine (3 mL). The flask under argon was cooled to -30°C. Slow addition of $POCl_3$ (0.30 mL, 3.16 mmol) gave after mixing a thick slurry. The slurry was mixed at -30°C for 3 h and the volatiles evaporated. Dichloromethane (5 mL) was then added and the insoluble solid was removed by filtration. The organic layer was washed with H_2O, 10% citric acid, brine and dried over Na_2SO_4. Removal of solvent gave crude desired nitrile (330 mg) (LC/Mass, + ion): 424 (M+H).

Step 4



Trifluoroacetic acid (3.3 mL) was added to a stirred solution of Step 3 compound (330 mg, 0.58 mmol) in 3.3 mL CH_2Cl_2. The solution was then stirred at rt for 30 min, a few drops of water were added and the mixture mixture stirred for 0.5 h. The mixture was diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20x100 mm column to give the title compound, 59 mg, 17%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/ 0.1 TFA

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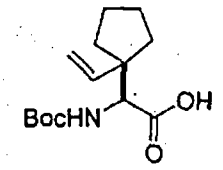
over 15 min; 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time 10 Min. (LC/Mass, + ion): 210 (M+H).

General Method B: Claisen rearrangement sequence to Boc-protected amino acids.



General method B affords the quaternary Boc-protected amino acids. Examples 30-47 contain the vinyl sidechain by coupling amino acids of which Scheme 4, compound **20** is representative. Cyclopentanone was olefinated under *Horner-Emmons conditions to afford* **17** *which was reduced* to the allylic alcohol **18** using DIBAL-H in toluene -78 °C to rt. Allylic alcohol **18** was esterified with N-Boc glycine using DCC/DMAP in CH_2Cl_2 to give **19**. Glycine ester **19** was subjected to a Lewis acid mediated Claisen rearrangement by complexation with anhydrous zinc chloride and deprotonation at -78°C with lithium diisopropylamide followed by warming to ambient temperature to afford **20**.

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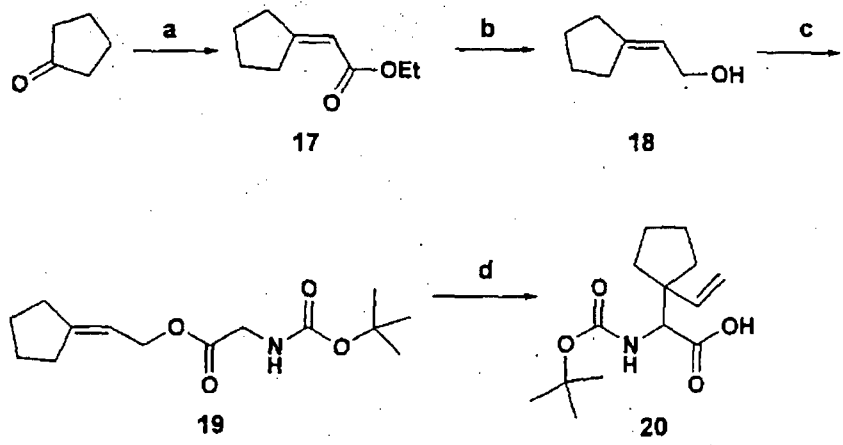
Scheme 4, General Method B, Examples 30-47



a. Triethylphosphonoacetate, NaH, THF O C to RT b. DIBAL-H, toluene, -78 C to RT c. N-Boc glycine, DCC, DMAP, CH_2Cl_2, RT
d. $ZnCl_2$, THF, LDA, -78 C to RT

Step 1

Cyclopentylideneacetic acid ethyl ester.

To a flame-dried 500-mL round-bottomed flask containing NaH (5.10 g of a 60% dispersion in mineral oil, 128 mmol, 1.10 equiv) in 120 mL anhydrous THF at 0°C under argon was added triethylphosphonoacetate (25.6 mL, 128 mmol, 1.10 equiv) dropwise through an addition funnel. The mixture was allowed to warm to rt, stirring for an additional 1 h. A solution of cyclopentanone (10.3 mL, 116 mmol) in 10 mL anhydrous THF was added dropwise over 20 min through an addition funnel, and the mixture was allowed to stir at rt for 2.5 h. Ether (200 mL) and water (100 mL) were then added, and the layers were separated. The organic phase was washed successively with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure, giving 17.5 g (98%) of the desired ester as a colorless oil.

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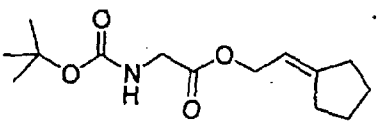
Step 2

2-Cyclopentylideneethanol.

To a flame-dried 500-mL round-bottomed flask containing cyclopentylideneacetic acid ethyl ester (17.5 g, 113 mmol) in 100 mL anhydrous toluene at -78°C under argon was added DIBAL-H (189 mL of a 1.5 M solution in toluene, 284 mmol, 2.50 equiv) dropwise over a 30 min period through an addition funnel, and the mixture was then allowed to warm to rt, stirring for 18 h. The reaction mixture was then recooled to -78°C, and quenched by the careful addition of 30 mL anhydrous MeOH. Upon warming to rt, 1 N Rochelle's salt (100 mL) was added, and the mixture was stirred 90 min. The biphasic reaction mixture was then diluted with Et_2O (200 mL) in a separatory funnel, and the layers were separated. The organic layer was then washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, CH_2Cl_2 / EtOAc, 10:1) gave 11.6 g (92%) of the desired allylic alcohol as a colorless oil.

Step 3

(2-Cyclopentylideneethyl)-N-(*tert*-Butyloxycarbonyl) glycinate.



To a flame-dried 500-mL round-bottomed flask containing N-(*tert*-butyloxycarbonyl)glycine (13.45 g, 76.75 mmol) in 100 mL CH_2Cl_2 at rt was added Step 2 compound (8.61 g, 76.75 mmol, 1.00 equiv) in 20 mL CH_2Cl_2, followed by dicyclohexylcarbodiimide (16.63 g, mmol, 1.05 equiv) in 80 mL CH_2Cl_2. To this reaction mixture was then added 4-

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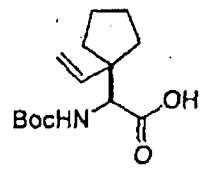
dimethylaminopyridine (0.94 mg, mmol, 0.10 equiv), and the mixture was allowed to stir overnight. The reaction mixture was then filtered through a medium sintered-glass funnel, rinsing with 100 mL CH_2Cl_2, and concentrated under reduced pressure. The crude product was then purified by flash chromatography (silica gel, hexanes/EtOAc, 20:1 to 1:1 gradient) to give 19.43 g (94%) of the desired glycinyl ester as a colorless oil.

Step 4

N-(*tert*-Butyloxycarbonyl)(1'vinylcyclopentyl)-glycine



A flame-dried 500-mL round-bottomed flask under argon was charged with $ZnCl_2$ (11.8 g, mmol, 1.20 equiv) and 20 mL toluene. The mixture was heated under vacuum with vigorous stirring to azeotrope off any traces of moisture with the distilling toluene, repeating this process (2 x). The flask was then cooled to rt under argon, (2-cyclopentylideneethyl) N-(*tert*-butyloxycarbonyl)glycinate (19.36 g, 71.88 mmol) was added via cannula as a solution in 180 mL THF, and the mixture was then cooled to -78°C. In a separate flame-dried 200-mL round-bottomed flask containing diisopropylamine (26.3 mL, mmol, 2.60 equiv) in 90 mL THF at -78°C was added n-butyllithium (71.89 mL of a 2.5 M solution in hexanes, mmol, 2.5 equiv), and the mixture was allowed to warm to 0°C for 30 min before recooling to -78°C. The lithium diisopropylamine thus generated was then added via cannula to the $ZnCl_2$ ester mixture dropwise at a steady rate over 40 min, and the

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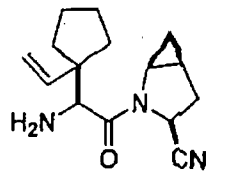
resultant reaction mixture was allowed to slowly warm to rt and stir overnight. The yellow reaction mixture was then poured into a separatory funnel, diluted with 300 mL Et_2O, and the resultant organic solution was washed successively with 300 mL 1N HCl and 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 3% MeOH in CH_2Cl_2 with 0.5% HOAc) gave 17.8 g (92%) of the desired amino acid product as a white solid. (FAB MH+ 270).

Example 30

General Method C: Peptide coupling to 4,5-methano-prolinamide, amide dehydration and final deprotection.



The TFA salt of amide **13** was coupled to a variety of racemic quaternary protected amino acids using HOBT/EDC in DMF at rt to give a D/L mixture of diastereomers at the N-terminal amino acid. The desired L diastereomer was chromatographically isolated either as the amide **21** or as the nitrile **22**. Nitrile **22** was obtained by treatment of the amide with $POCl_3$/imidazole in pyridine at -20°C. The final target **23** was obtained by deprotection under acidic conditions using TFA in CH_2Cl_2.

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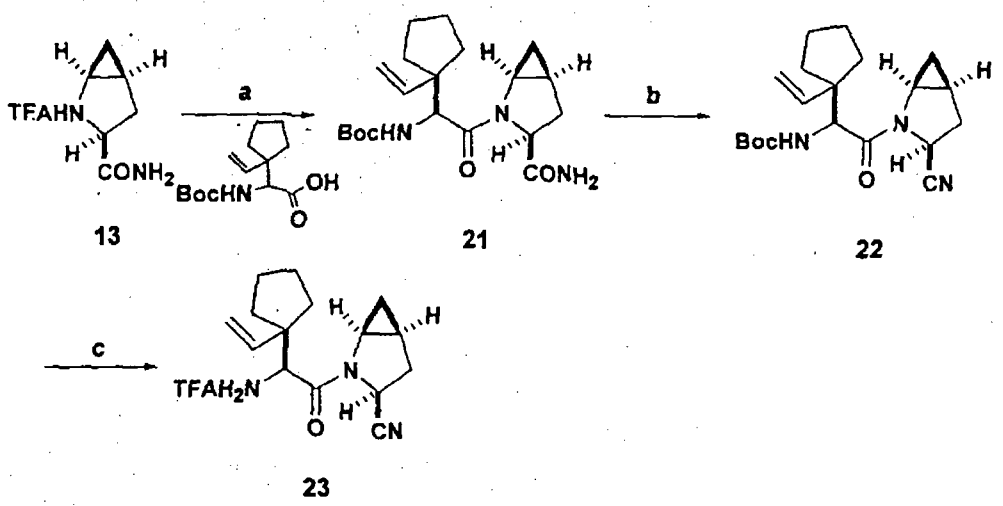
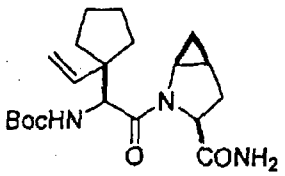
Scheme 5, General Method C



13 21 22 23

a. EDAC, HOBT, DMF b. $POCl_3$, pyridine, imidazole, -20C c.TFA, CH_2Cl_2, RT

Step 1



Example 6 Step 3 compound (877 mg, 3.65 mmol) and N-Boc cyclopentylvinylamino acid, described in Step 4 of general method B (1.13 g, 4.20 mmol) were dissolved in 20 mL anhydrous DMF, cooled to 0°C and to this mixture was added EDAC (1.62 g, 8.4 mmol), HOBT hydrate (2.54 g, 12.6 mmol, and TEA (1.27 g, 12.6 mmol) and the reaction was allowed to warm to rt and stirred for 24 h. The reaction mixture was taken up in EtOAc (100 mL), washed with H_2O (3 x 20 mL), dried (Na_2SO_4), and purified by silica gel flash column chromatography (100% EtOAc) to give 1.38 g (86%) of Step 1 compound (MH+, 378).

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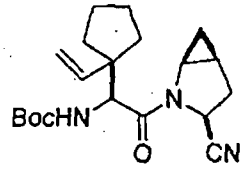
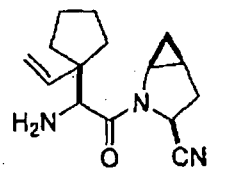
Step 2



Step 1 compound (1.38 g, 3.65 mmol) and imidazole (497 mg, 7.30 mmol) were dried by toluene azeotrope (5 mL x 2), dissolved in 10 mL anhydrous pyridine, cooled to -30°C under nitrogen gas and $POCl_3$ (2.23 g, 14.60 mmol) was added by syringe. The reaction was complete after 1 h and was evaporated to dryness and the remainder purified by two sequential flash column chromatographies over silica gel. The first column (100% EtOAc) was used to isolate the mixture of diastereomers (1.15 g, 88%) from the by-products of the reaction. The second column (gradient of 25% EtOAC/hexanes to 50% EtOAc/hexanes) was run to resolve the mixture of diastereomers and provided 504 mg of the desired Step 2 nitrile (MH+360).

Step 3



Step 2 compound (32 mg, 0.09 mmol) was dissolved in 1 mL of CH_2Cl_2 and 1 mL of TFA was added and the reaction stirred for 30 min at rt and was evaporated to dryness. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20 X 250 mm column to give 12 mg of the TFA salt (lyophilized from water or isolated after evaporation of eluent and trituration with ether) the title compound. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90%

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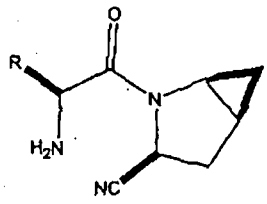
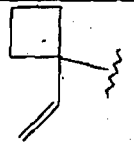
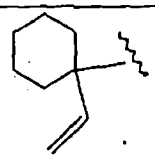
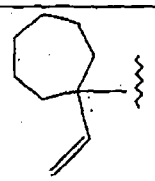
methanol/water/0.1 TFA over 18 min; 5 min. hold at 90% methanol/water/0.1 trifluoroacetic acid. Flow rate: 20 mL/min. Detection wavelength: 220.

Examples 30-39 were prepared by the methods outlined in General Method B and General Method C starting from cyclopentanone, cyclobutanone, cyclohexanone, cycloheptanone, cyclooctanone, cis-3,4-dimethylcyclopentanone, and 4-pyranone, cyclopropaneethylhemiacetal, acetone, and 3-pentanone respectively.

Table 2



Example	R	MS [M + H]
30		260
31		246
32		274
33		288

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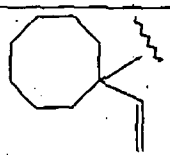
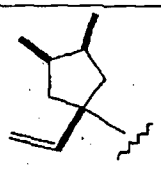
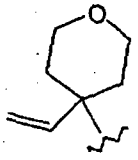
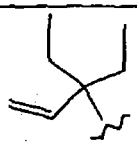
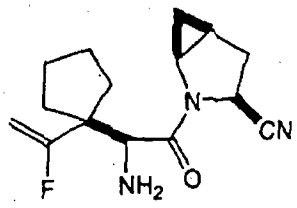
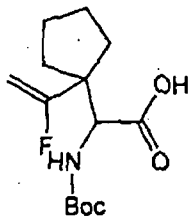
34		302
35		288
36		276
37*		232
38		234
39		262

* Step 3 compound was prepared by the method described in Tetrahedron Letters 1986, 1281-1284.

Example 40



Step 1



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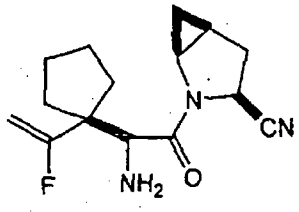
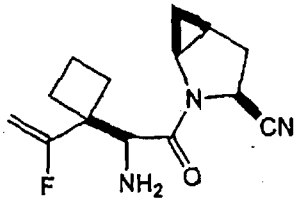
Step 1 compound was prepared employing general method B starting from cyclopentanone and 2-fluoro-triethylphosphonoacetate instead of triethylphosphonoacetate.

Step 2

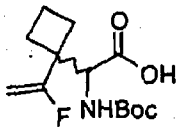


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C [MS (M+H) 278].

Example 41



Step 1



Step 1 compound was prepared employing general method B starting from cyclobutanone and 2-fluoro-triethylphosphonoacetate instead of triethylphosphonoacetate.

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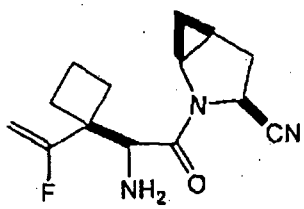
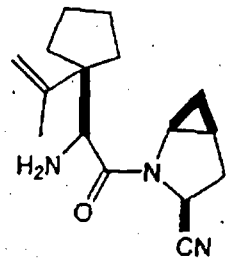
Step 2

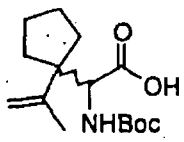


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 264.

Example 42



Step 1



Step 1 compound was prepared employing general method B starting from cyclopentanone and triethylphosphono-propionate instead of triethylphosphonoacetate.

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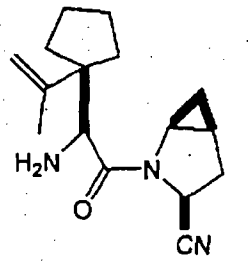
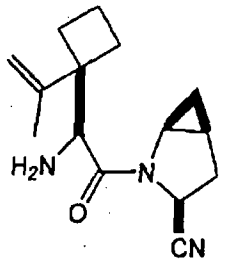
Step 2

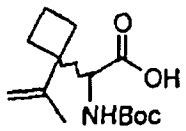


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 274

Example 43



Step 1



Step 1 compound was prepared employing general method B starting from cyclobutanone and triethylphosphono-propionate instead of triethylphosphonoacetate.

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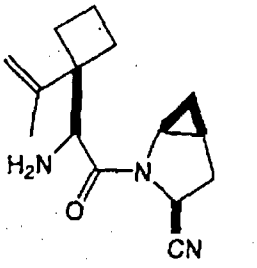
Step 2

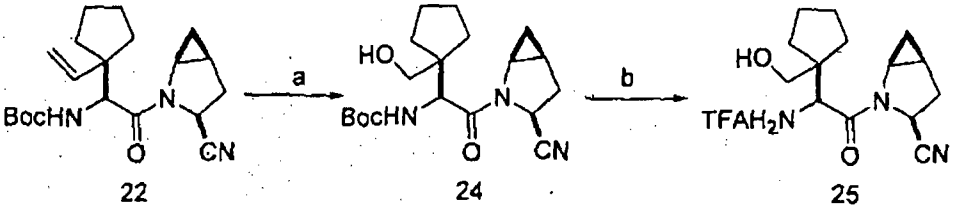


Title compound was prepared by the peptide coupling of Step 1 acid followed by dehydration and final deprotection as described in general method C. MS (M+H) 260.

Example 44

General Method D: *Oxidative cleavage of vinyl* substituent by ozonolysis. The protected cyclopentylvinyl nitrile **22** was treated with ozone for 6-8 min and subjected to a reductive quench with sodium borohydride to furnish the hydroxymethyl analog **24** directly. This compound was deprotected under acidic conditions with TFA in CH_2Cl_2 at 0°C to give the target compound **25**.

Scheme 6, General Method D, Examples 44,46,48



a. O_3, MeOH:CH_2Cl_2, 10:4, -78 C; then $NaBH_4$, -78 C to 0 C, 79%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C.

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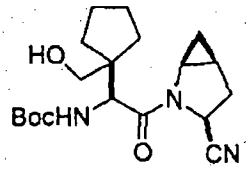
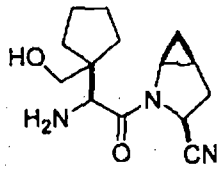
Step 1



Cyclopentylvinyl compound prepared in Step 2 of general method C (1.28 g, 3.60 mmol) was dissolved in 56 mL of a 2:5 mixture of CH_2Cl_2:methanol, cooled to -78°C and was treated with a stream of ozone until the reaction mixture took on a blue color, at which time, $NaBH_4$ (566 mg, 15.0 mmol, 4.2 equiv) was added and the reaction was warmed to 0°C. After 30 min, the reaction was quenched with 2 mL saturated aqueous $NaHCO_3$ and then warmed to rt. The reaction mixture was evaporated to dryness and taken up in EtOAc. A small amount of water was added to dissolve the inorganics and the layers separated. The EtOAc layer was dried (Na_2SO_4), filtered and evaporated to an oil that was purified by flash column chromatography on silica gel with EtOAc to give 922 mg (71%) of Step 1 compound. MS(M+H)364.

Step 2



Step 1 compound (900 mg, 2.48 mmol) was dissolved in 60 mL of CH_2Cl_2, cooled to 0°C and treated with 20 mL of freshly distilled TFA. The reaction was complete in 80 min and the mixture was evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30 x 100 mm, 18 minute gradient 80% Solv A:Solv B to 100% Solv B, Solvent A = 10% MeOH-90%H_2O-0.1% TFA, Solvent B = 90% MeOH-10%

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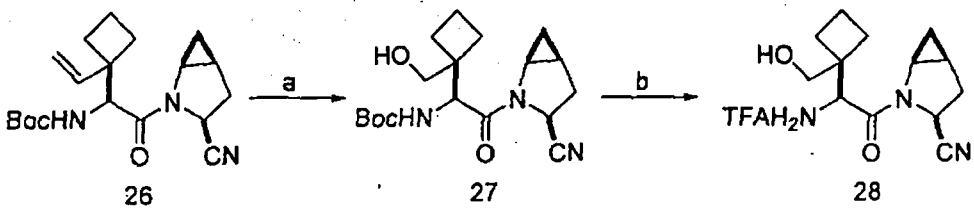
H_2O -.1% TFA, collected product from 5.1-6.5 min) to give, after lyophillization from water, 660 mg (71%) of title compound, TFA salt as a white lyophillate. (MH+264).

Example 45

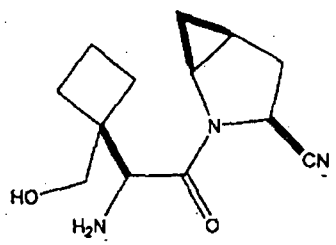
General Method E: Oxidative cleavage of vinyl substituent by osmium tetroxide-sodium periodate followed by sodium borohydride reduction to alcohol. The cyclobutylolefin **26** was treated with osmium tetroxide and sodium periodate in THF:water, 1:1, and the intermediate aldehyde was isolated crude and immediately reduced with sodium borohydride to give **27** in 56% yield. Standard deprotection conditions using TFA afforded the target compound **28**.

Scheme 7, General Method E, Examples 45, 47



26 27 28

a.OsO_4, THF:H_2O, 1:1; $NaIO_4$; workup,then $NaBH_4$, MeOH, RT. 56%
b. TFA:CH_2Cl_2, 1:2, 0 degrees C to RT.



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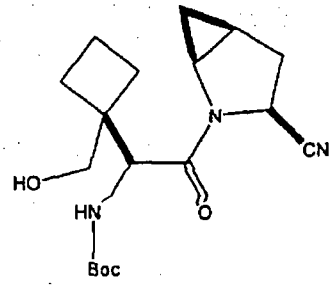
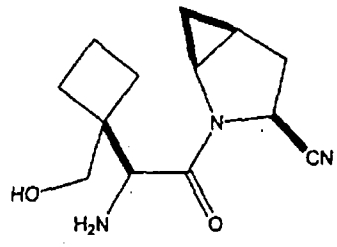
Step 1



N-Boc protected cyclobutylvinyl compound (Example 31, prepared by general method C) (0.16 g, 0.46 mmol) was dissolved in 10 mL of a 1:1 mixture of THF:water and treated with OsO_4 (12 mg, catalyst) and $NaIO_4$ (0.59 g, 2.76 mmol, 6 equiv). After 2 h, the reaction mixture was diluted with 50 mL of ether and 10 mL of water. The layers were equilibrated and the organic fraction was washed one time with $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give a dark oil. The oil was diluted with 10 mL of methanol and treated with $NaBH_4$ (0.08 g, 2.0 mmol). The mixture turned very dark and after 30 min was diluted with ether and the reaction was quenched with aqueous $NaHCO_3$ solution. The mixture was equilibrated and layers separated. The organic fraction was washed with solutions of $NaHCO_3$ and 0.1 M HCl. The organics were dried ($MgSO_4$) and concentrated to give 90 mg (56%) of the Step 1 compound as a dark oil.

Step 2



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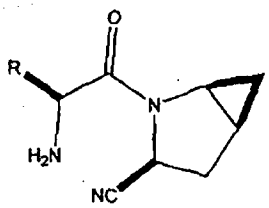
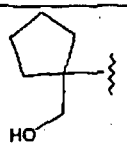
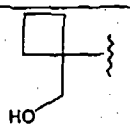
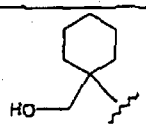
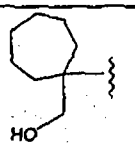
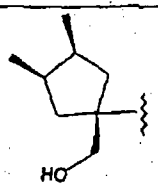
Step 1 compound (90 mg, 0.26 mmol) was dissolved in 3 mL of CH_2Cl_2, cooled to 0°C and treated with 3 mL of freshly distilled TFA. The reaction was complete in 80 min and evaporated to dryness and purified by preparative HPLC (YMC S5 ODS 30 x 100 mm, 10 minute gradient 100%A to 100%B, Solvent A = 10% MeOH-90%H2O-0.1% TFA, Solvent B = 90% MeOH-10% H_2O -0.1% TFA, to give, after removal of water, 50 mg (60%) of title compound. (MH+250).

Table 3



Example	R	Method of Preparation	[M + H]
44		Ozonolysis/ borohydride	264
45		Osmium/periodate/ borohydride	250
46		Ozonolysis/ borohydride	278
47		Osmium/periodate/ borohydride	292
48		Ozonolysis/ borohydride	292

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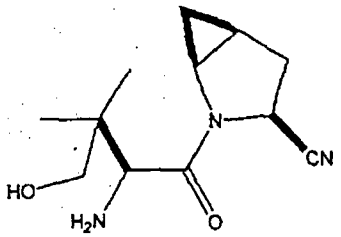
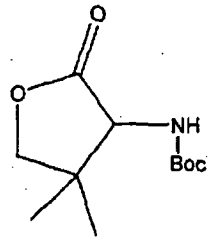
Example 49



Step 1



Part A. A 50-mL flask was charged with dihydro-4,4-dimethyl-2,3-furandione (5.0 g, 39.0 mmol), acetic acid (10 mL), sodium acetate (3.82 g, 39.0 mmol) and hydroxylamine hydrochloride (2.71 g, 39.0 mmol). The reaction mixture was stirred for 2 h at rt and concentrated under reduced pressure to remove most of the acetic acid. The remainder was poured into water (100 mL) and the aqueous phase extracted with EtOAc (3 X 40 mL). The organics were dried over Na_2SO_4 and concentrated to a colorless oil which solidified on standing.

Part B. A 200-mL round bottomed flask was charged with Part A solid (@ 39 mmol) and diluted with 80 mL of ethanol and 39 mL of 2N HCl (78 mmol). The mixture was treated with 1.0 g of 5% Pd/carbon and the mixture degassed. The flask was placed under an atmosphere of H_2 for 8 h. The mixture was filtered through celite and the filtrate concentrated to an off white solid.

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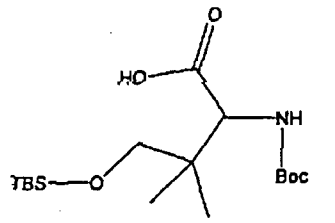
Part C. A 250-mL round bottomed flask was charged with Part B solid and diluted with THF (50 mL) and water (15 mL). The mixture was treated with di-*tert*-butyldicarbonate (12.7 g, 117 mmol) and sodium bicarbonate (10.0 g, 117 mmol). After 4 h of stirring the mixture was diluted with 50 mL of ether and 50 mL of water. The layers were separated and the organic fraction dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel with 30% EtOAc in hexanes to give 2.00 g (22% overall) of Step 1 compound as a white solid.

Step 2



To a stirred solution of Step 1 compound (1.00 g, 3.80 mmol) in THF (20 mL) at rt under nitrogen was added LiOH hydrate (0.16 g, 3.80 mmol) and then water (5 mL). The reaction was stirred at 40°C for 0.5 h and then cooled to rt. The mixture was concentrated to dryness and the remainder was stripped from THF (2X), toluene (2X) and THF (1X). The remaining glass was diluted with 5 mL of THF and treated with imidazole (0.63 g, 9.19 mmol) followed by t-butyl-dimethylsilyl chloride (1.26 g, 8.36 mmol). The reaction was stirred overnight and quenched with 10 mL of methanol. After 1 h of stirring the mixture was concentrated. An additional portion of methanol was added and the mixture concentrated. The oil was diluted with ether and 0.1 N HCl (pH 2). The layers were equilibrated and aqueous drawn off. The organic

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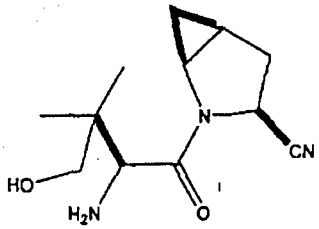
fraction was dried over $MgSO_4$ and concentrated to give 1.25 g (83%) of Step 2 compound as a colorless glass.

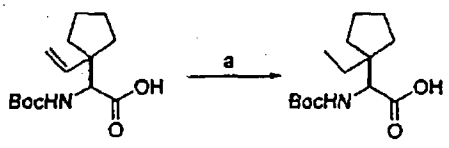
Step 3



The Title compound was prepared by the peptide coupling of Step 2 carboxylic acid with Example 6 Step 3 amine, followed by dehydration and deprotection as outlined in General Method C. MS (M+H) 238.

General Method F: Catalytic Hydrogenation of vinyl substituent. As shown in Scheme 8, the protected vinyl substituted amino acid **20** was transformed to the corresponding saturated analog **29** by catalytic hydrogenation using 10% Pd/C and hydrogen at atmospheric pressure.

Scheme 8, General Method F, Examples 50-56



20 29

a. 10% Pd/C, 1 atm H_2, MeOH, 12h, 100%

Step 1.

The N-(*tert*-Butyloxycarbonyl)(1'vinylcyclopentyl)glycine (2.23 g, 8.30 mmol) was dissolved in 50 mL MeOH and placed in a hydrogenation vessel purged with argon. To this mixture was added 10% Pd-C (224 mg, 10% w/w) and the reaction stirred under 1 atm H_2 at rt for 12 h. The reaction was filtered through celite and concentrated and

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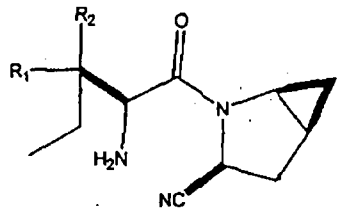
purified by flash column chromatography on silica gel with 1:9 methanol:CH_2Cl_2 to give the Step 1 compound as a glass. (FAB MH+ 272)

Examples 50-56 were prepared by the peptide coupling of amino acids (where the vinyl substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C.

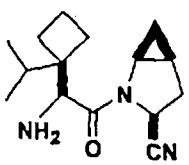
Table 4



Example	R1, R2	MS [M + H]
50	Cyclopentyl	262
51	cyclobutyl	248
52	cycloheptyl	290
53	4-pyranyl	278
54	methyl, methyl	236
55	ethyl, ethyl	264
56	methyl, ethyl	250

15

Example 57



The title compound in Example 57 was prepared by the peptide coupling of the isopropyl cyclobutane amino acid

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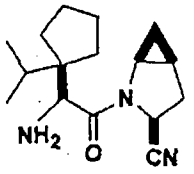
(where the olefin substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C.

Example 58



The title compound in Example 58 was prepared by the peptide coupling of the isopropyl cyclopentane amino acid (where the olefin substituent has been hydrogenated according to general method F) followed by dehydration and deprotection as described in general method C. MS (M+H) 276

General Method G: L-Amino acids synthesized by Asymmetric Strecker Reaction. Commercially available adamantyl carboxylic acid was esterified either in MeOH with HCl at reflux or using trimethylsilyldiazomethane in Et_2O/methanol to give **30**. The ester was reduced to the alcohol **31** with LAH in THF and then subjected to a Swern oxidation to give aldehyde **32**. Aldehyde **32** was transformed to **33** under asymmetric Strecker conditions with KCN, $NaHSO_3$ and R-(-)-2-phenylglycinol. The nitrile of **33** was hydrolyzed under strongly acidic conditions using 12M HCl in HOAc to give **34**. The chiral auxiliary was removed by catalytic reduction using Pearlman's catalyst in acidic methanol under 50 psi hydrogen to give **35** and the resulting amino group was protected as the t-butylcarbamate to give **36**.

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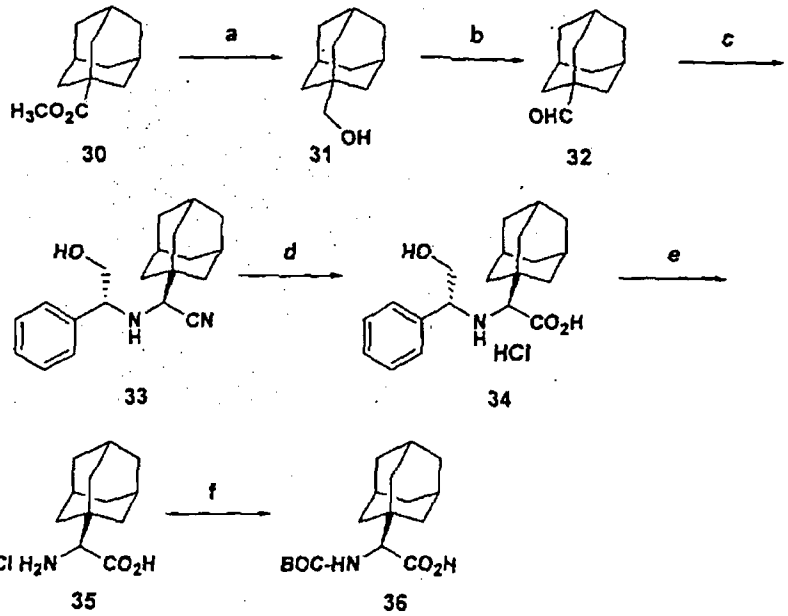
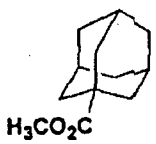
Scheme 9, General Method G, Examples 59-64



a. LAH, THF, 0 C to RT, 95% b. ClCOCOCl, DMSO, CH_2Cl_2, -78 C, 98% c. R-(-)-2-Phenylglycinol, $NaHSO_3$, KCN d.12M HCl, HOAc, 80 C, 16h, 78 % e. 20% $Pd(OH)_2$, 50 psi H_2, MeOH:HOAc, 5:1 f. $(Boc)_2O$, K_2CO_3, DMF, 92%, 2 steps

Step 1



Adamantane-1-carboxylic acid (10.0 g, 55 mmol, 1 equiv) was dissolved in a mixture of Et_2O (160 mL) and MeOH (40 mL), and was treated with trimethylsilyl diazomethane (2.0 M in hexane, 30 mL, 60 mmol, 1.1 equiv) and stirred at rt for 3 h. The volatiles were then removed by rotary evaporation and the product purified by flash column chromatography on silica gel (5x15 cm) with 40% CH_2Cl_2/hexanes to give the product as a white crystalline solid (10.7 g, 100%).

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Step 2

Step 1 compound (10.7 g, 0.055 mmol, 1 equiv) was dissolved in anhydrous THF (150 mL) under argon and was treated with a solution of $LiAlH_4$ (1 M in THF, 69 mL, 69 mmol, 1.25 equiv). After stirring at rt for 1.5 h, the reaction was cooled to 0°C and quenched sequentially with H_2O (5.1 mL), 15% aq NaOH (5.1 mL), and H_2O (10.2 mL). After stirring at rt for 15 min, the slurry was vacuum filtered, and the solids washed with EtOAc (2x100 mL). The filtrate was concentrated by rotary evaporation and the resulting solid purified by flash column chromatography on silica gel (5x15 cm) with 10% EtOAc/CH_2Cl_2. This afforded the Step 2 product as a white solid (8.74 g, 96%).

Step 3

An oven-dried 3-neck flask equipped with 125-mL addition funnel was charged with anhydrous CH_2Cl_2 (150 mL) and anhydrous DMSO (10.3 mL, 0.145 mol, 2.5 equiv) under argon atmosphere and cooled to -78°C. Slow dropwise addition of oxalyl chloride (6.7 mL, 0.0768 mol, 1.32 equiv) followed by stirring for 15 min provided an activated DMSO adduct. This was treated with a solution of Step 2 compound (9.67 g, 58.2 mmol, 1 equiv) in dry CH_2Cl_2 (75 mL) and the reaction allowed to stir for 1 h. The resulting white mixture was then treated dropwise with triethylamine (40.5 mL, 0.291 mol, 5 equiv). After

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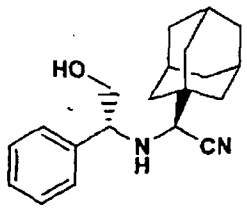
30 min, the cooling bath was removed, and the reaction quenched sequentially with cold 20% aq KH_2PO_4 (25 mL) and cold H_2O (150 mL). After stirring at rt for 15 min the mixture was diluted with Et_2O (400 mL)and the layers were separated. The organics were washed organic with cold 10% aq KH_2PO_4 (3x150 mL) and satd aq NaCl (100 mL). The organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography on silica gel (5x10 cm) with CH_2Cl_2 to give the Step 3 compound as a white solid (9.40 g, 98%).

Step 4



Step 3 compound (9.40 g, 57 mmol, 1 equiv) was suspended in H_2O (145 mL) and cooled to 0°C. The mixture was treated with $NaHSO_3$ (5.95 g, 57 mmol, 1 equiv), KCN (4.0 g, 59 mmol, 1.04 equiv), and a solution of (*R*)-(-)-phenylglycinol (8.01 g, 57 mmol, 1 equiv) in MeOH (55 mL). The resulting mixture was stirred at rt for 2 h, then refluxed for 16 h. The mixture was cooled to rt, and 200 mL of EtOAc added. After mixing for 15 min the layers were separated. The aqueous fraction was extracted with EtOAc. The combined EtOAc extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated. The product was purified by flash column chromatography on silica gel (6.4x20 cm) with 20% EtOAc/hexanes to give the desired (R,S) product as a white solid (11.6 g, 37.4 mmol, 65%): MS m/e 311 $(M+H)^+$.

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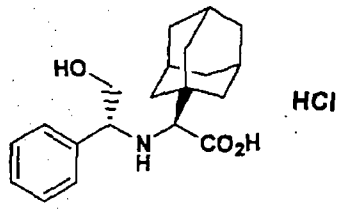
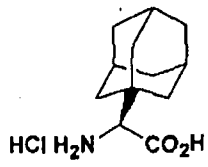
Step 5



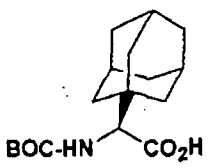
The Step 4 nitrile (5.65 g, 18 mmol) was heated in conc. HCl (120 mL) and HOAc (30 mL) at 80°C for 18 h, at which time the reaction was cooled in an ice bath. Vacuum filtration of the resulting precipitate afforded the desired product as a white solid (5.21 g, 14 mmol, 78%). MS m/e 330 $(m+H)^+$.

Step 6



The Step 6 compound (5.21 g, 14 mmol) was dissolved in MeOH (50 mL) and HOAc (10 mL), and hydrogenated with H_2 (50 psi) and Pearlman's catalyst (20% $Pd(OH)_2$, 1.04 g, 20% w/w) for 18 h. The reaction was filtered through a PTFE membrane filter and the catalyst washed with MeOH (3x25 mL). The filtrate was concentrated by rotary evaporation to afford a white solid. The product was used in Step 7 without further purification.

Step 7



The crude Step 6 compound (@ 14 mmol) was dissolved in anhydrous DMF (50 mL) under argon and treated with K_2CO_3

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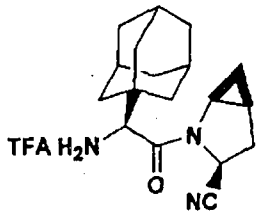
(5.90 g, 42 mmol, 3 equiv) and di-*tert*-butyldicarbonate (3.14 g, 14 mmol, 1 equiv) under argon at rt. After 19 h, the DMF was removed by rotary evaporation (pump) and the residue dried further under reduced pressure. The residue was mixed with H_2O (100 mL) and Et_2O (100 mL), the layers separated, and the alkaline aqueous with Et_2O (2x100 mL) to remove the by-product from the hydrogenolysis step. The aqueous was cooled to 0°C, diluted with EtOAc (200 mL), and stirred vigorously while carefully acidifying the aqueous to pH 3 with 1N aq HCl. The layers separated and the aqueous extracted with EtOAc (100 mL). The combined EtOAc extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and the filtrate concentrated by rotary evaporation. The residue was purified by SiO_2 flash column (5x12 cm) with 5% $MeOH/CH_2Cl_2$ + 0.5% HOAc. The product was chased with hexanes to afford the product as a white foam (4.07 g, 13 mmol, 92%): MS m/e 310 $(m+H)^+$.

Example 59



The title compound in Example 59 was prepared by the peptide coupling of the Step 7 compound in general method G followed by dehydration and deprotection as described in general method C. MS m/e 300 $(m+H)^+$.

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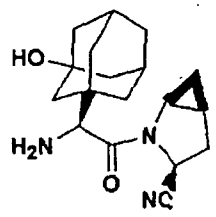
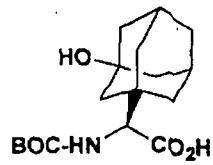
Example 60

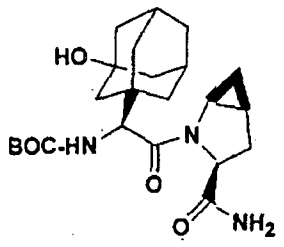


Step 1



A solution of $KMnO_4$ (337 mg, 2.13 mmol, 1.1 equiv) in 2% aq KOH (6 mL) was heated to 60°C and Step 7 compound in general method G (600 mg, 1.94 mmol, 1 equiv) was added in portions, and heating increased to 90°C. After 1.5 h, the reaction was cooled to 0°C, EtOAc (50 mL) was added, and the mixture was carefully acidified to pH 3 with 1N HCl. The layers were separated and the aqueous was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (3.8x15 cm) with 2% (200 mL), 3% (200 mL), 4% (200 mL), and 5% (500 mL) $MeOH/CH_2Cl_2$ + 0.5% HOAc. After isolation of the product, the material was chased with hexanes to afford a white solid (324 mg, 51%): MS m/e 326 $(m+H)^+$.

Step 2



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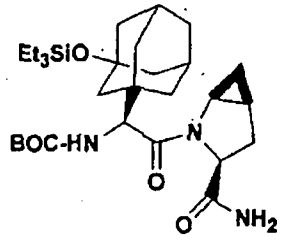
The Step 1 compound (404 mg, 1.24 mmol, 1 equiv) was dissolved in anhydrous DMF (10 mL) under argon and cooled to 0°C. The following were added in order: Example 6 Step 3 salt (328 mg, 1.37 mmol, 1.1 equiv), HOBT (520 mg, 3.85 mmol, 3.1 equiv), EDAC (510 mg, 2.61 mmol, 2.1 equiv), and TEA (0.54 mL, 3.85 mmol, 3.1 equiv). The reaction mixture was allowed to warm to rt overnight and the DMF removed by rotary evaporation (pump). The remainder was dried further under vacuum. The residue was dissolved in EtOAc (100 mL), washed with satd aq $NaHCO_3$ (50 mL) and satd aq NaCl (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation. The product was purified flash column chromatography on silica gel (3.8x15 cm) with a gradient of 6% (200 mL), 7% (200 mL), and 8% (500 mL) MeOH/CH_2Cl_2 to give the product as a white solid (460 mg, 1.06 mmol, 85%): MS m/e 434 $(m+H)^+$.

Step 3



The Step 2 compound (95 mg, 0.22 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) under argon and cooled to -78°C. The mixture was treated with diisopropylethylamine (65 µL, 0.37 mmol, 1.7 equiv), and triethylsilyl triflate (75 µL, 0.33 mmol, 1.5 equiv), and stirred at 0°C for 1.5 h. The reaction was mixed with MeOH (0.5 mL), silica gel (200 mg) and H_2O (2 drops) and stirred at rt for 18 h. The solvent was removed by rotary evaporation and the residue purified flash column

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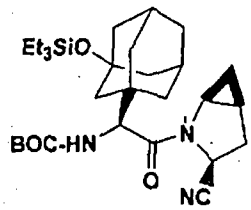
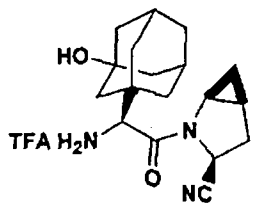
chromatography on silica gel(2.5x10 cm) with 4% MeOH/CH_2Cl_2 to afford the product (92 mg, 0.17 mmol, 77% MS m/e 548 $(m+H)^+$.

Step 4



The Step 3 compound (90 mg, 0.16 mmol, 1 equiv) was dissolved in anhydrous pyridine (2 mL) under argon and cooled to -30°C. Treatment with imidazole (24 mg, 0.35 mmol, 2.1 equiv) and phosphorous oxychloride (66 µL, 0.67 mmol, 4.1 equiv), and continued stirring at -30°C for 45 min gave a thick slurry. Volatiles were by rotary evaporation and the cake dried further under reduced pressure. The product was purified by flash column chromatography on silica gel (2.5x10 cm) with 7% EtOAc/CH_2Cl_2 to afford the product as a white foam (76 mg, 87%): MS m/e 530 $(m+H)^+$

Step 5



The Step 4 compound (76 mg, 0.14 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0°C and treated with TFA (1 mL) and H_2O (2 drops) and stirred for 1.5 hr at 0°C. The solvents were removed by rotary evaporation and the residue was chased with toluene (5 mL) and dried

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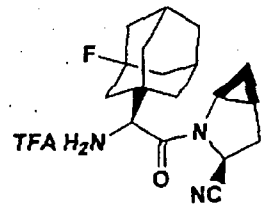
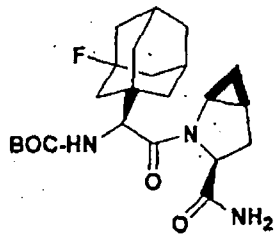
under reduced pressure. Trituration with Et_2O afforded the title compound as a white solid (54 mg, 88%): MS m/e 316 $(m+H)^+$.

Example 61



Step 1



An oven-dried flask purged with argon was charged with anhydrous CH_2Cl_2 (3 mL) and cooled to -78°C. Treatment with diethylaminosulfur trifluoride (DAST, 60 µL, 0.45 mmol, 1.5 equiv), followed by a solution of the Example 60 Step 2 compound (131 mg, 0.30 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL). After 15 min, the reaction was poured into a separatory funnel containing satd aq $NaHCO_3$ (25 mL) and the layers were separated. The aqueous fraction was extracted with CH_2Cl_2 (25 mL), then the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (2.5x10 cm) with 5% MeOH/CH_2Cl_2 to give Step 1 compound (124 mg, 0.29 mmol, 94%): MS m/e 436 $(m+H)^+$.

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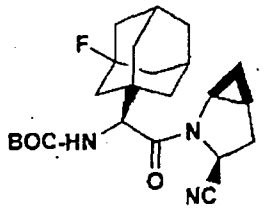
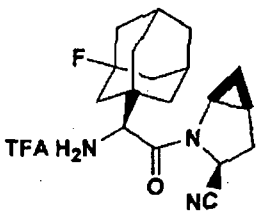
Step 2



The fluorinated amide from Step 1 (161 mg, 0.37 mmol, 1 equiv) was dissolved in anhydrous pyridine (4 mL) under argon and cooled to -30°C. The mixture was treated with imidazole (54 mg, 0.77 mmol, 2.1 equiv) and phosphorous oxychloride (143 µL, 1.52 mmol, 4.1 equiv) and stirred at -30°C for 40 min. The solvent was removed by rotary evaporation and dried further under reduced pressure. The product was purified by flash column chromatography on silica gel(2.5x10 cm) with 5% EtOAc/CH_2Cl_2 to give the Step 2 compound as a white foam (126 mg, 82%): MS m/e 418 $(m+H)^+$.

Step 3



The Step 2 compound (125 mg, 0.30 mmol) was dissolved in TFA/CH_2Cl_2 (1:1 v/v, 2 mL), and stirred at rt. After 30 min, the solvents were removed by rotary evaporation, the remainder was chased with toluene (2x5 mL), and the solid dried under reduced pressure. Trituration with Et_2O afforded the title compound as a white solid (93 mg, 0.21 mmol, 72%): MS m/e 318 $(m+H)^+$.

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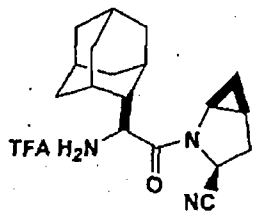
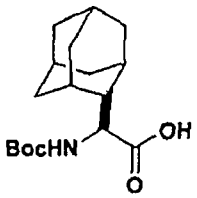
Example 62

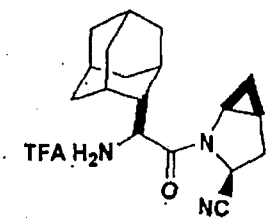


Step 1



The Step 1 compound was prepared beginning with 2-adamantanal and elaborated to the homochiral Boc-amino acid by an asymmetric Strecker synthesis according to general method G.

Step 2



The title compound in Example 62 was prepared by the peptide coupling of the 2-adamantyl amino acid described in Step 1 followed by dehydration and deprotection as described in general method C.MS (M+H) 300.

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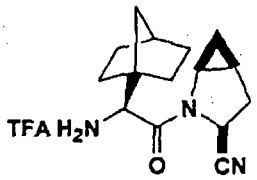
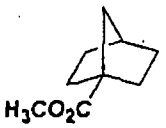
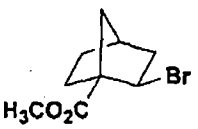
Example 63



Step 1



An oven-dried flask equipped with a condenser and drying tube was charged with norbornane-2-carboxylic acid (4.92 g, 35 mmol, 1 equiv) and treated with bromine (2.1 mL, 41 mmol, 1.15 equiv) and phosphorous trichloride (0.153 mL, 1.8 mmol, 0.05 equiv). The mixture was heated at 85°C for 7 h protected from light. Additional bromine (0.4 mL, 7.8 mmol, 0.22 equiv) was added with continued heating for 1 h. The mixture was cooled to rt, and Et_2O (100 mL) was added. The mixture was washed with 10% aq $NaHSO_3$ (50 mL), H_2O (2x50 mL), and brine (25 mL). The ether fraction was dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The product was purified by flash column chromatography on silica gel (5x15 cm) with 2% to 4% MeOH/CH_2Cl_2 + 0.5% HOAc. The product was chased with hexanes to remove residual HOAc. The isolated material consists of two inseparable materials (4.7 g), which was used without further purification in the next step.



The crude product from above, exo-2- bromonorbornane-1-carboxylic acid (4.7 g, impure) in Et_2O (80 mL) and MeOH (20 mL), was mixed with trimethylsilyldiazomethane (2.0 M in hexane, 11.8 mL, 23.6 mol), and stirred at rt for 1 h.

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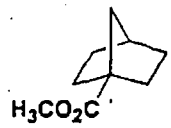
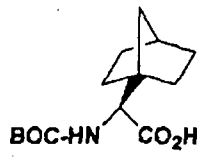
Solvent was removed by rotary evaporation, and purification of the oil by flash column chromatography on silica gel (5x18 cm) with a gradient of CH_2Cl_2/hexanes (600 mL each of 20% and 30%) followed by CH_2Cl_2 afforded the product as a white solid (3.97 g, 0.017 mol, 79% for 2 steps): MS m/e 233/235 $(m+H)^+$.



Methyl exo-2-bromonorbornane-1-carboxylate (2.0 g, 8.58 mmol, 1 equiv) was dissolved in anhydrous THF (50 mL) in an oven-dried 3-neck flask equipped with a condenser, and purged with argon. The mixture was treated with AIBN (288 mg, 1.71 mmol, 0.2 equiv) and tributyltin hydride (3.6 mL, 12.87 mmol, 1.5 equiv), and then heated to reflux for 2 h. The flask was cooled to rt, and the THF was removed by rotary evaporation to give the crude product. The product was purified by flash column chromatography on silica gel(5x10 cm) with 5% EtOAc/hexanes. The resulting material was used in the next step without further purification.

Step 2



The Step 1 compound was prepared beginning with 1-norbonyl methyl carboxylate and elaborated to the homochiral Boc amino acid by an asymmetric Strecker synthesis according to general method G.

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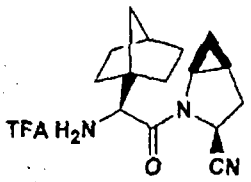
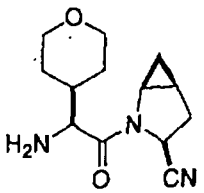
Step 3

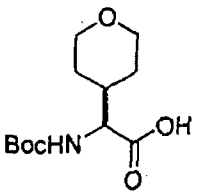


The title compound in Example 63 was prepared by the peptide coupling of the 1-norbonyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 260.

Example 64

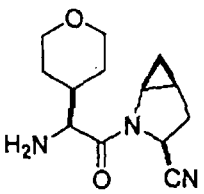


Step 1



The Step 1 compound was prepared beginning with 4-formylpyran and elaborated to the homochiral Boc amino acid by an asymmetric Strecker synthesis according to general method G.

Step 2



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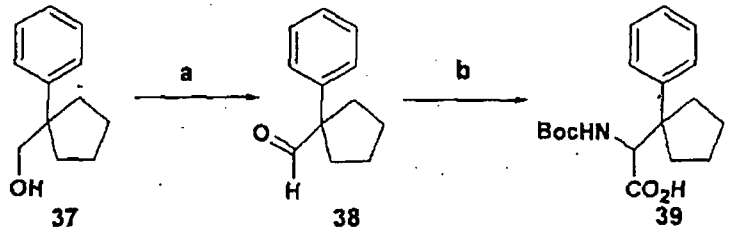
The title compound in Example 64 was prepared by the peptide coupling of the 4-pyranyl amino acid described in Step 2, followed by dehydration and deprotection as described in general method C. MS (M+H) 250.

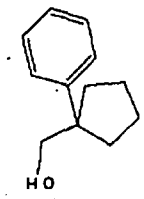
General Method H: Strecker Synthesis of Racemic Amino Acids.

Scheme 10, General Method H, Examples 65-66



a. celite, PCC, CH_2Cl_2, RT, 91% b. NH_4Cl, NaCN, MeOH; 12M HCl, HOAc; $(Boc)_2O$, TEA, DMF.

Step 1



To a stirred solution of 1-phenylcyclo-1-pentane-carboxylic acid (5.00 g, 26.3 mmol) in 25 mL of THF at 0°C was added LAH (52 mL , 52 mmol, 1M) in THF. The reaction mixture was slowly warmed to rt and then refluxed for 18 h. The reaction was quenched according to the Fieser procedure: careful addition of 2 mL of water; 6 mL of 15% NaOH in water; and 2 mL of water. The biphasic mixture was diluted with 100 mL of ether and the granular white solid filtered off. The ether fraction was dried over Na_2SO_4 and evaporated to give 4.30 g (93%) of the Step 1 compound.

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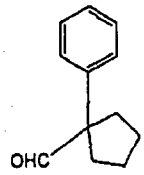
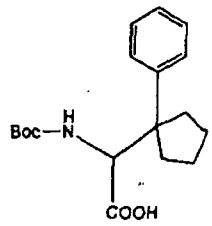
Step 2



To a stirred solution of Step 1 compound (0.80 g, 4.50 mmol) in 15 mL of CH_2Cl_2 at rt was added celite (5 g) followed by PCC (1.95 g, 5.00 mmol). After stirring for 3 h the reaction mixture was diluted with 40 mL of CH_2Cl_2 and filtered through celite. The filtrate was filtered an additional time through silica gel resulting in a colorless filtrate. The CH_2Cl_2 fraction was evaporated to give 0.72 g (91%) of the aldehyde as a colorless oil.

Step 3



To a 50-mL round-bottomed flask containing Step 2 compound (0.72 g, 4.20 mmol) in 8 mL of water at rt was added NaCN (0.20 g, 4.20 mmol) followed by NH_4Cl (0.20 g, 5.00 mmol). To this reaction mixture was then added methanol (8 mL) and the mixture was allowed to stir overnight. The reaction mixture was then extracted with ether (2X15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude Strecker product.

To a 100-mL round-bottomed flask containing the crude Strecker product was added 10 mL of HOAc and 10 mL of conc. HCl. The mixture was refluxed overnight. The mixture was concentrated under reduced pressure to give a

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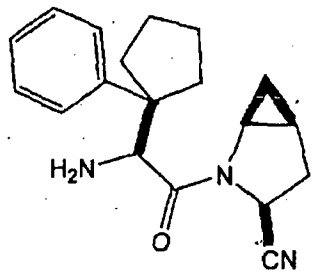
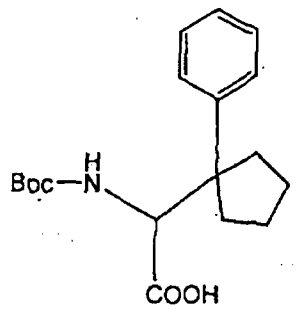
yellow solid. The solid was triturated with 5 mL of 1:1 mixture of ether and hexanes. The white solid was treated with triethylamine (1.4 mL, 9.99 mmol) and di-*tert*-butyldicarbonate (1.00 g, 4.60 mmol) in 50 mL DMF. After 4 h the pH of the mixture was adjusted to 9 with saturated Na_2CO_3 soln. After an additional 3 h of stirring the mixture was extracted with 1:1 ether and hexanes and the aqueous fraction acidified to pH 2 with 5% $KHSO_4$ solution. The aqueous phase was washed with ether (2 X 40 mL), the organics dried ($MgSO_4$), and evaporated to an oil that was purified by silica gel flash chromatography with 8:92 methanol:CH_2Cl_2 to give 0.3 g (23%) of the Boc-protected amino acid as a light oil (M-H, 318).

Example 65



Step 1



The synthesis of the Step 1 compound was described in general method H for the Strecker synthesis of racemic amino acids.

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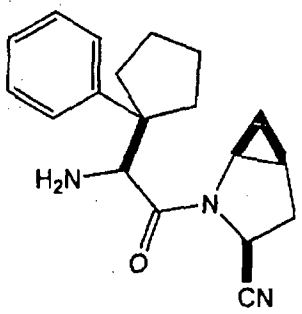
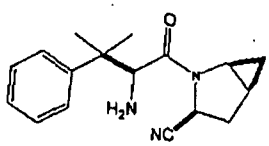
Step 2

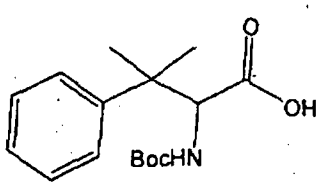


The title compound in Example 65 was prepared by the peptide coupling of the cyclopentylphenyl amino acid described in Step 1 and general method H followed by dehydration and deprotection as described in general method C. MS (M+H) 310.

Example 66

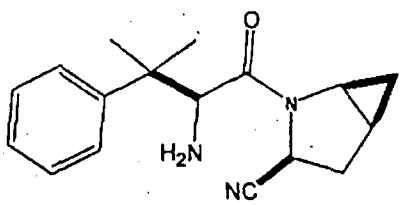


Step 1



Step 1 compound was prepared using racemic Strecker synthesis according to general method H starting from 2,2-dimethyl-phenylacetic acid.

Step 2



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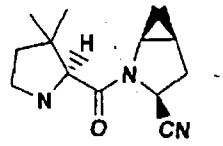
The title compound in Example 66 was prepared by the peptide coupling of the dimethylphenyl amino acid described in step 1 followed by dehydration and deprotection as described in general method C. MS (M+H) 264.

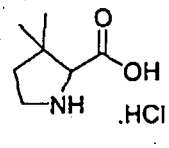
Example 67



Step 1

N-(Benzyloxycarbonyl) succinimide (5.6 g, 22.4 mmol) was dissolved in CH_2Cl_2 (25 mL) and the solution was added to a cooled (0°C) and stirred solution of diethyl aminomalonate hydrochloride (5.0 g, 23.6 mmol) and triethylamine (13.4 mL, 95 mmol) in CH_2Cl_2 (125 ml). The resulting solution was stirred at 0°C for 10 min and then at rt for 1 h. The solution was washed with 10% citric acid (2 x 50 mL), 10% sodium hydrogen carbonate (2 x 50 mL), and water (50 mL) and was then dried (Na_2SO_4) and evaporated to afford diethyl N-benzyloxycarbonylamino malonate as a colorless oil, which crystallized upon standing at 0°C (6.3 g) (LC/Mass + ion):310 (M+H).

Step 2



Step 1 compound (6.18 g, 20 mmol) was dissolved in dry ethanol (30 mL) and added to a solution of sodium ethoxide (2.85 g, 8.8 m mol; 21% w/w solution in ethanol (6 mL). A solution of 3-methyl-2-butenal (1.68 g, 20

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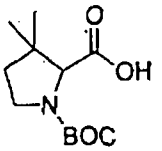
mmol) in ethanol (12 mL) was added, and the solution stirred at 25°C for 24 h. Acetic acid (0.56 mL) was then added the solution hydrogenated at 50 psi for 24 h using 10% Pd/C (2.0 g) as catalyst. The solution was filtered, evaporated and the residue chromatographed on silica with CH_2Cl_2 / EtOAc (9:1) to give 2,2-dicarboethoxy-3,3-dimethyl-pyrrolidine (1.6 g) (LC/Mass, + ion): 244 (M+H).

This diester (850 mg) was refluxed in 5 M hydrochloric acid (10 mL)/TFA (1 mL) for 8 h to give, after evaporation, a powdery white solid. Crystallization from methanol/ether gave 3,3-dimethyl-dl-proline hydrochloride (190 mg) as white crystals mp 110-112°C.

Step 3



Step 2 compound (173 mg, 0.97 mmol) was dissolved in DMF (3 mL)/ water (3 mL). To this clear solution was added triethylamine (0.46 mL, 3.18 mmol) and di-t-butyl dicarbonate (0.23 g, 1.06 mmol), and the reaction mixture was stirred at rt for 5 h. The solution was evaporated and the residue chromatographed on silica column using CH_2Cl_2/methanol (9:1) as eluent to yield t-butyloxy-carbonyl-3,3-dimethyl-dl-proline (200 mg) as an oil (LC/Mass, + ion): 244 (M+H).

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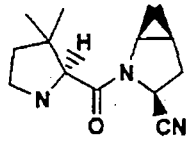
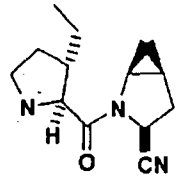
Step 4

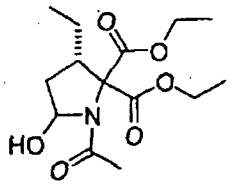


The title compound in Example 67 was prepared by the peptide coupling of the t-butyloxycarbonyl-3,3-dimethyl-dl-proline amino acid described in Step 3 followed by dehydration and deprotection as described in general method C. MS (M+H) 220.

Example 68



Step 1



Sodium ethoxide (940 mg of 21 wt% solution in ethanol, 2.9 mmol) in ethanol (2 mL) was added to a stirred solution of diethyl acetamidomalonate (4.31g, 19.8 mmol) in EtOH (23 mL) at rt under argon. The reaction mixture was cooled to 0°C, and trans-2-pentenal (1.51 g, 18.0 mmol) was added dropwise maintaining the reaction temperature at < 5°C. After the addition, the reaction was allowed to warm to rt, stirred for 4 h, then quenched with acetic acid (460 µl). The solution was concentrated in vacuo, and the residue dissolved in EtOAc (25 mL), washed with 10% $NaHCO_3$ solution (2x5 mL), brine and dried ($MgSO_4$). The solution was filtered and concentrated to a

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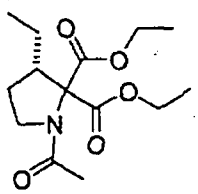
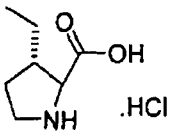
10 mL volume, then heated to reflux and diluted with hexane (20 mL). Upon cooling to rt, the title compound precipitated and was collected to give 3.0 g (50%) of the Step 1 compound (mp 106-109°C; LC/Mass: + ions, 324 M+Na).

Step 2



To a solution of Step 1 compound (2.87 g, 9.5 mmol) and triethylsilane (2.28 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) under argon was added TFA (7.35 mL, 95.3 mmol) dropwise with stirring while maintaining the internal temperature at 25°C by means of an ice bath. After stirring for 4 h at rt, the solution was concentrated. The residue was diluted with CH_2Cl_2 (100 mL), then treated with H_2O (50 mL) and solid Na_2CO_3 with vigorous stirring until the mixture was basic. The organic layer was separated, dried (Na_2SO_4), filtered, then concentrated to give the Step 2 compound as a yellow oil which was used without further purification (LC/Mass: + ions, 308 M+Na).

Step 3



Step 2 compound (3.73 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was then cooled, washed with EtOAc (20 mL), then concentrated to give an oil which crystallized upon trituration with ether to give the

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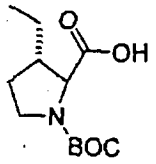
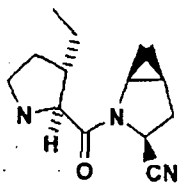
title compound (1.2 g, 70.6%) (LC/Mass, + ion): 144 (M+H).

Step 4



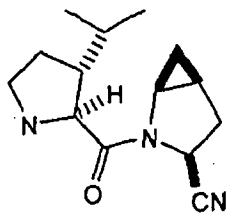
Step 3 compound (692 mg, 3.76 mmol) was dissolved in acetone (12 mL)/ water (12 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-*t*-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solvents were evaporated and the residue chromatographed on silica with 1:9 methanol:CH_2Cl_2 to give the Step 4 compound as an oil (LC/Mass: + ions, 266 M+Na).

Step 5



Example 68 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 234).

Example 69



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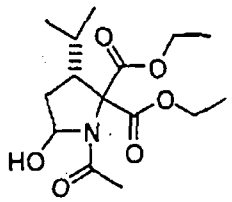
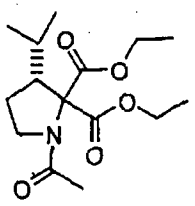
Step 1



Sodium ethoxide (940 mg, 2.9 mmol; 21% w/w solution in ethanol) in ethanol (2 mL) was added to a stirred solution of diethyl acetamidomalonate (4.31 g, 19.8 mmol) in EtOH (23 mL) at rt under argon. The reaction mixture was cooled to 0°C; and 4-methyl-2-pentenal (1.77 g, 18.0 mmol)was added dropwise maintaining the reaction temperature at < 5°C. After the addition, the reaction was allowed to warm to rt, stirred for 4 h, then quenched with acetic acid (460 µl). The solution was concentrated and the remainder dissolved in EtOAc (25 mL). The organics were washed with 10% $NaHCO_3$ solution (2x5 mL), brine and dried ($MgSO_4$). The solution was filtered and concentrated to 10 mL volume, then heated to reflux and treated with hexane (20 mL). On cooling, the Step 1 compound precipitated and was collected (3.3 g) (LC/Mass, + ion): 338 (M+Na).

Step 2



To a solution of Step 1 compound (3.0g, 9.5 mmol) and triethylsilane (2.28 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) under argon was added TFA (7.35 mL, 95.3 mmol) dropwise with stirring while maintaining the internal temperature at 25°C, by means of an ice bath. After stirring for 4 h

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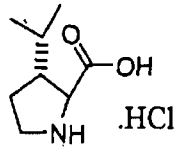
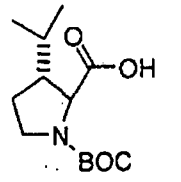
at rt, the solution was concentrated, the residue diluted with CH_2Cl_2 (100 mL), then treated with H_2O (50 mL) and solid Na_2CO_3 with vigorous stirring until the mixture was basic. The organic layer was separated, dried (Na_2SO_4), filtered, then concentrated to give the title compound as an oil which was used without further purification (LC/Mass:+ ions, 300 M+H).

Step 3



Step 2 compound (3.8 g, 9.5 mmol) was suspended in 6 N HCl (20 mL) and HOAc (5 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (20 mL), then concentrated to give an oil which crystallized upon trituration with ether to give the step 3 compound (1.4 g, 76.0%). LC/Mass: + ions, 158 (M+H).

Step 4



Step 3 compound (728 mg, 3.76 mmol) was dissolved in a 1:1 acetone/water solution (24 mL). To this clear solution was added triethylamine (1.9 mL, 12.8 mmol) and di-*t*-butyl dicarbonate (928 mg, 4.24 mmol). The reaction mixture was stirred at rt for 18 h. The solution was evaporated and the residue chromatographed on silica column using CH_2Cl_2/ methanol (9:1) as eluent to give the title compound as an oil (LC/Mass, + ion): 258 (M+H).

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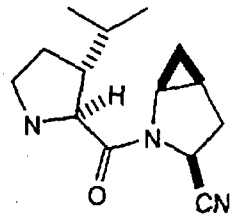
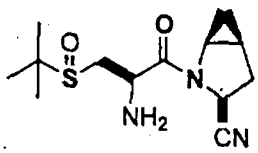
Step 5

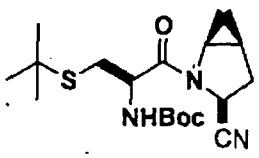


Example 69 compound was prepared by peptide coupling of Step 4 amino acid followed by dehydration and deprotection as described in general method C (MS (M+H) 248).

Example 70

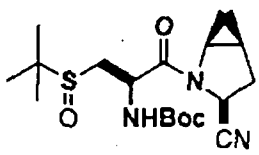


Step 1



Step 1 compound was prepared by the procedure described in General Method C starting from N-Boc-S-t-butylcysteine.

Step 2



A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with Step 1 compound

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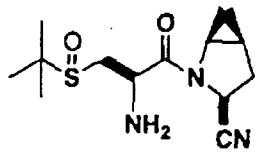
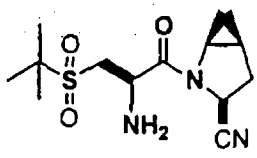
(78 mg, 0.21 mmol) and chloroform (3 mL). The mixture was cooled to 0°C and treated with *m*-chloroperoxybenzoic acid (85 mg, 0.44 mmol) in $CHCl_3$ (2 mL). After 3 h the solution was diluted with $CHCl_3$ (7 mL), washed with 5% $NaHCO_3$ (2x5 mL), H_2O and dried over Na_2SO_4. Removal of solvent gave crude sulfoxide (100 mg), which was used without further purification (LC/Mass, + ions): 384 (M+H).

Step 3



Trifluoroacetic acid (1.5 mL) was added to a cooled (0°C) solution of Step 2 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was then stirred at 0°C for 1.5 h, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20x100 mm column to give the title compound of Example 70 , 17 mg, 16%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/ 0.1 TFA over 15 min 5 min hold at 90% methanol/water/0.1 TFA. Flow rate: 20 mL/min. Detection wavelength: 220. Retention Time 10 Min (LC/Mass, + ion): 284 (M+H).

Example 71



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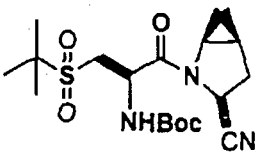
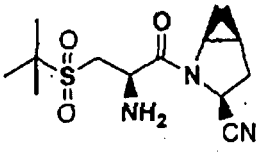
Step 1



A 25-mL round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet was charged with compound from Example 70, Step 1 (78 mg, 0.21 mmol) in chloroform (3 mL). The mixture was cooled to 0°C and treated with *m*-chloroperoxybenzoic acid (144 mg, 0.84 mmol) in $CHCl_3$ (2 mL). After 30 min at rt, the solution was diluted with $CHCl_3$ (7 mL), washed with 5% $NaHCO_3$ (2x10 mL), H_2O and dried over Na_2SO_4. Removal of solvent gave the crude sulfone (100 mg), which was used without further purification (LC/Mass, + ion): 344 (M+H-Bu).

Step 2



Trifluoroacetic acid (1.5 mL) was added to a cooled (0°C) and stirred solution of Step 1 compound (100 mg, 0.26 mmol) in 5 mL CH_2Cl_2. The solution was stirred at 0°C for 30 min, diluted with CH_2Cl_2 (5 mL) and concentrated under reduced pressure to a thick oil. The product was purified by reverse phase preparative column chromatography on a YMC S5 ODS 20x100 mm column to give the title compound, 14 mg, 17%. Purification conditions: gradient elution from 10% methanol/water/0.1 TFA to 90% methanol/water/ 0.1 TFA over 15 min. 5 min hold at 90% methanol/water/0.1 TFA. Flow rate:20 mL/min. Detection

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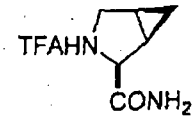
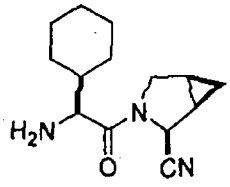
wavelength: 220. Retention Time 10 Min. (LC/Mass, + ion): 300 (M+H).

Example 72



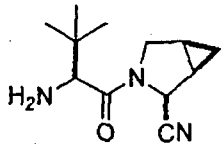
The title compound was prepared following a published procedure (Sasaki et al, Tetrahedron Lett. 1995, 36, 3149, Sasaki et al. Tetrahedron 1994, 50, 7093) used to synthesize (2S,3R,4S)-N-Boc-3,4-methano-L-proline carboxylate. The corresponding amide was prepared by general method A and deprotected with TFA to give the TFA salt also as described in general method A.

Example 73



The title compound was prepared by coupling (2S,3R,4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-cyclohexylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+ 248).

Example 74



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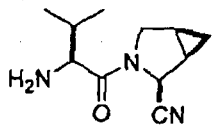
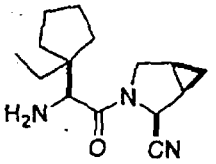
The title compound was prepared by coupling (2S,3R,4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-*tert*-butylglycine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH^+ 222).

Example 75



The title compound was prepared by coupling (2S,3R,4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with L-valine and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+ 207).

Example 76



The title compound was prepared by coupling (2S,3R,4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(tert-butyloxycarbonyl)-(1'ethylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using general C (FAB MH+ 262).

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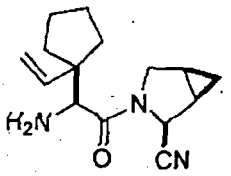
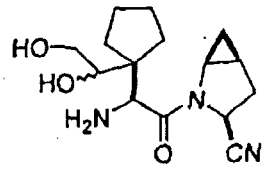
Example 77.



The title compound was prepared by coupling (2S,3R,4S)-3,4-methano-L-proline carboxamide-N-trifluoroacetate described in Example 72 with N-(*tert*-butyloxycarbonyl)-(1'vinylcyclopentyl)glycine described in General Method B and then dehydrated to the amide with $POCl_3$/imidazole and deprotected (N-terminal nitrogen) with TFA using General Method C (FAB MH+ 260).

Example 78



N-[((S)-cyclopentylvinyl)-N-tert-butoxycarbonylglycinyl]-(2S,4S,5S)-2-cyano-4,5-methano-L-prolylamide (70 mg, 0.19 mmol) described in General Method C, Step 2 was dissolved in a mixture of 2 mL *t*-BuOH / 3 mL *THF* and N-methylmorpholine-N-oxide (33mg, 0.28 mmol) was added followed by osmium tetroxide (0.1 mmol, 50 mol%). The reaction was quenched with 1 mL of 10% aqueous Na_2SO_3 and was taken up in EtOAc and washed with H_2O 5 mL, dried (Na_2SO_4), filtered, evaporated and purified by silica gel flash chromatography (5% MeOH/CH_2Cl_2) to give 41 mg (55%) of the protected diol as an oil. The title compound was obtained by deprotection of the amine functionality with TFA according to General Method C (FAB MH+ 294).

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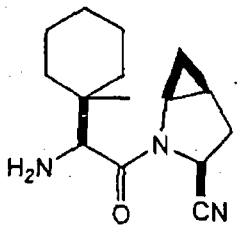
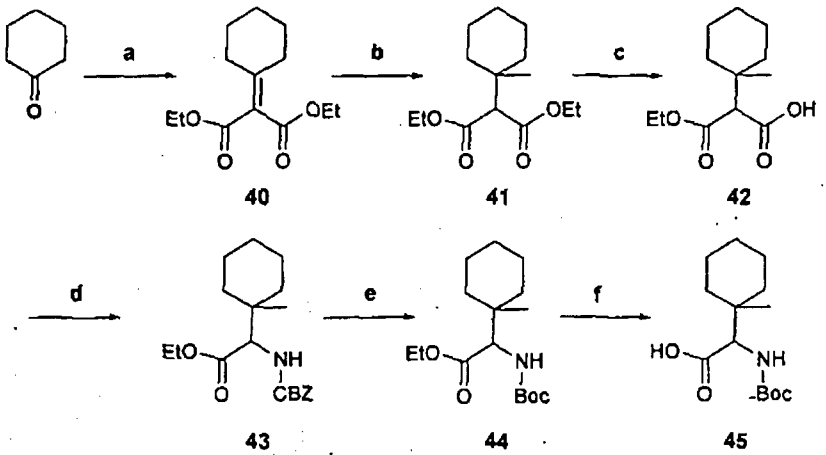
Example 79



General Procedure I: Synthesis of Quaternary Amino Acids Via Michael Addition to Malonates followed by Selective Hydrolysis and Curtius Rearrangement. Examples 79-84.

Cyclohexanone and diethylmalonate underwent Knoevenagel condensation mediated by titanium tetrachloride in THF and CCl_4 to give **40**. Copper (I) mediated Grignard addition of methylmagnesium bromide gave **41** which was selectively saponified to **42**. Curtius rearrangement with trapping by benzyl alcohol gave **43** which was converted to **44** by a standard deprotection-protection protocol. Ester **44** was saponified to give the quaternary amino acid **45**.

Scheme 11, General Method I



a. THF, CCl_4, $TiCl_4$, diethylmalonate, 0 C; pyridine, THF, 0 to RT 72 h b. MeMgBr, CuI, Et_2O, 0 C c. 1N NaOH, EtOH, RT 6 days d. Ph_2PON_3, TEA, RT to reflux to RT, BnOH e. 10% $Pd(OH)_2/C$, EtOAc; $(Boc)_2O$, K_2CO_3, THF f. IN NaOH, dioxane

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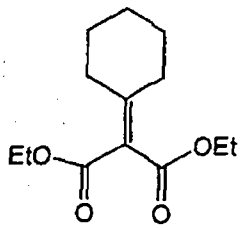
Step 1



According to literature procedure (Tetrahedron 1973, 29, 435), a mixture of dry tetrahydrofuran (400 mL) and dry carbon tetrachloride (50 mL) was cooled to 0°C (ice-salt bath) and treated with titanium tetrachloride (22.0 mL, 0.2 mole). The resulting yellow suspension was stirred at 0°C for 5 min, treated sequentially with cyclohexanone (10.3 mL, 0.1 mole) and distilled diethylmalonate (15.2 mL, 0.1 mole) then stirred at 0°C for 30 min. The reaction mixture was then treated with a solution of dry pyridine (32 mL, 0.40 mole) in dry THF (60 mL), stirred at 0°C for 1.0 h, then at rt for 72 h. The reaction mixture was quenched with water (100 mL), stirred for 5 min then extracted with ether (2 x 200 mL). The combined organic extracts were washed with saturated sodium chloride (100 mL), saturated sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography using 5% EtOAc in hexane gave step 1 compound as a light yellow oil. Yield: 5.25 g (22%). MS (M + Na) 263.

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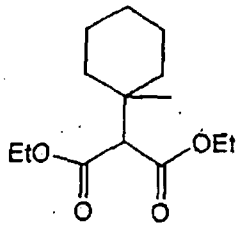
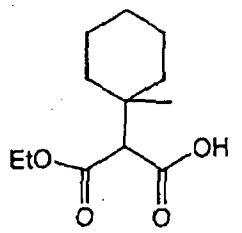
Step 2



According to literature (Org. Syn. VI, 442, 1988; Liebigs Ann. Chem. 1981, 748) a mixture of 3.0 M methylmagnesium iodide (3.1 mL, 9.36 mmol) and cuprous chloride (9.0 mg) was stirred at 0°C (ice-salt water bath), treated with a solution of Step 1 compound (1.5 g, 6.24 mmol) in dry ether (1.8 mL) over 5 min and stirred at 0°C for 1 h, then at rt for 40 min. The mixture was slowly added to a slurry of ice and water (15 mL), treated dropwise with 10% HCl (3.7 mL) then extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with 1% sodium thiosulfate (2.0 mL) and saturated sodium chloride (2.0 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography on a silica gel column using 5% ether in hexane (1.0 L) gave step 2 compound as a clear syrup. Yield: 1.09 g, (68%). MS (M+H) 257.

Step 3



A solution of Step 2 compound (1.09 g, 4.03 mmol) in a mixture of methanol (5.4 mL) and water (2.7 mL) was treated with 1N sodium hydroxide (4.84 mL, 4.84 mmol or

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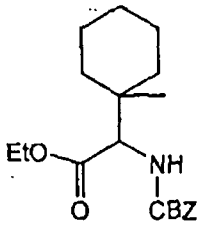
1.2 equiv) and stirred at rt for 6 days. The reaction mixture still showed the presence of starting material, so THF (4.0 mL) was added and the entire mixture stirred for another 2 days. The solution was evaporated to dryness and the resulting syrup partitioned between water (8.0 mL) and ether (15 mL). The aqueous phase was acidified with 1N hydrochloric acid (4.8 mL) to pH 2-3 and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give step 3 compound as a thick syrup. Yield: 875 mg, (95.1%). MS (M + H) 229.

Or alternately: solutions of the diester in a mixture of ethanol, THF, dioxane and water or mixtures thereof may be hydrolyzed with sodium hydroxide.

Step 4



According to literature (J. Org. Chem 1994, 59, 8215), a solution of Step 3 compound (0.875 g, 3.83 mmol) in dry benzene (4.0 mL) was treated with triethylamine (0.52 mL, 3.83 mmol) and diphenylphosphoryl azide (0.85 mL, 3.83 mmol), refluxed under nitrogen for 1 h and cooled to rt. The solution was treated with benzyl alcohol (0.60 mL, 5.75 mmol or 1.5 equiv), refluxed for 17 h, cooled then diluted with ether (40 mL). The solution was washed with 10% aqueous citric acid (2x3 mL),back-extracting the citric acid wash with ether (40 mL). The combined

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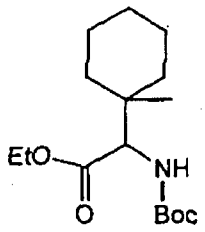
organic extracts were washed with 5% sodium bicarbonate (2x3 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of the crude product with 10% EtOAc in hexane (1.0 L) gave step 4 compound as a clear thick syrup. Yield: 1.15 g (90%). MS(M+H) 334.

Step 5



A solution of Step 4 compound (1.15 g, 3.46 mmol) in EtOAc (60 mL) was treated with palladium hydroxide on carbon (298 mg) and hydrogenated at rt for 20 h. The mixture was filtered through a celite pad and then washing the pad well with EtOAc (3 x 25 mL) then the filtrate was concentrated to give the free amine. A solution of the amine in tetrahydrofuran (12 mL) and water (12 mL) was treated with di-*t*-butyl dicarbonate (1.0 g, 4.58 mmol or 1.48 equiv) and potassium carbonate (854 mg, 6.18 mmol or 2.0 equiv), then stirred at rt for 20 h. The reaction mixture was partitioned between water (8 mL) and diethyl ether (3 x 40 mL) and the combined organic extracts were washed with brine (8 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the crude product with 10% EtOAc in hexane (1 L) gave step 5 compound as a clear thick syrup. Yield: 1.18 g (100%). MS:(M+H) 300.

Other methods can also be employed, for example: According to Tetrahedron Lett. 1988, 29, 2983, where a solution of the benzylcarbamate in ethanol may be treated

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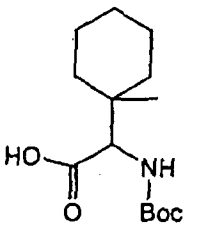
with triethylsilane (2 equiv), di-*t*-butyldicarbonate (1.1 equiv), catalytic palladium acetate and triethylamine (0.3 equiv) to give the BOC-protected amine in a "one-pot" manner.

Or alternately: Solutions of the benzylcarbamate in methanol may be subjected to hydrogenolysis in the present of di-*t*-butyldicarbonate to give the BOC-protected amine in a "one-pot" manner.

Step 6



A solution of Step 5 compound (1.18 g, 3.09 mmol) in dioxane (8.0 mL) was treated with 1N sodium hydroxide (9.1 mL, 9.1 mmol or 3.0 equiv) and stirred at 60°C (oil bath) for 28 h. The reaction mixture was concentrated to a syrup which was dissolved in water (15 mL) and extracted with ether (25 mL). The aqueous phase was acidified to pH 2-3 with 1N hydrochloric acid (9.2 mL) then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with saturated sodium chloride (10 mL), dried ($MgSO_4$), filtered, and concentrated to give Step 6 compound as an off-white solid. Yield: 808 mg (96%). MS (M+H) 272.

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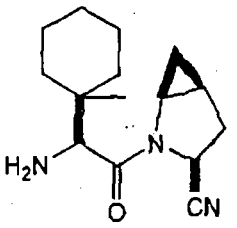
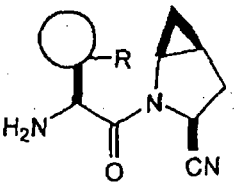
Step 7



The title compound was prepared from Step 6 compound according to the procedure in General Method C where the amino acid was coupled, the amide was dehydrated, and the protecting group removed to give the title compound. MS (M+H) 262.

Compounds 90-100 were prepared by General Method I and General Method C starting from cyclohexanone, cyclopentanone and cyclobutanone, and employing methyl-, ethyl-, allyl- and propylmagnesium halides as Grignard reagents.

Table 5



Example #	Cycloalkane	R	MS Data M+H
79	cyclohexane	Methyl	262
80	cyclohexane	Ethyl	276
81	cyclopentane	Methyl	248
82	cyclopentane	Allyl	274
83	cyclopentane	Propyl	276
84	cyclobutane	Methyl	234

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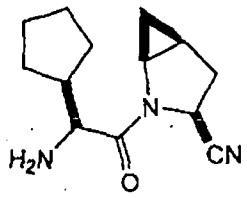
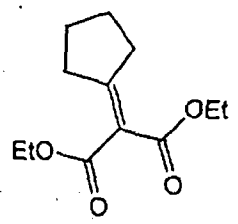
Example 85



Step 1



According to Example 79: A mixture of dry carbon tetrachloride (50 mL) was cooled to 0°C (ice-salt bath) and treated with titanium tetrachloride (11.0 mL, 0.1 mol). The resulting yellow suspension was stirred at 0°C for 5 min, treated sequentially with cyclopentanone (4.42 mL, 0.05 mol) and distilled diethylmalonate (7.6 mL, 0.05 mol) then stirred at 0°C for 30 min. The reaction mixture was then treated with a solution of dry pyridine (16 mL, 0.20 mol) in dry THF (30 mL), stirred at 0°C for 1.0 h, then at rt for 20 h. The reaction mixture was quenched *with water (50 mL), stirred for 5 min then extracted with* ether (2 x 100 mL). The combined organic extracts were washed with saturated sodium chloride (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography using 5% EtOAc in hexane gave Step 1 compound as a light yellow oil. Yield: 7.67 g (68%). MS (M + H) 226.

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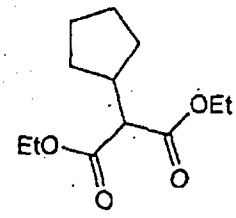
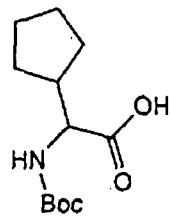
150

Step 2



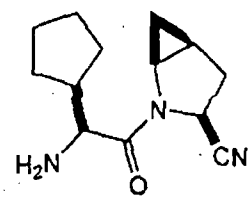
A solution of Step 1 compound (1.00 g, 4.42 mmol) in methanol (50 mL) was treated with 10% Pd/C (0.20 g, 10 mol%) and hydrogenated (balloon pressure) at rt for 20 h. The mixture was diluted with methanol and filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography on silica gel with 7% EtOAc in hexanes to give 0.84 g (91%) of Step 2 compound. MS (M+H) 229.

Step 3



The Step 3 compound was prepared by the process outlined in General Method H, where the ester underwent hydrolysis, Curtius Rearrangement, protecting group exchange, and again final ester hydrolysis.

Step 4



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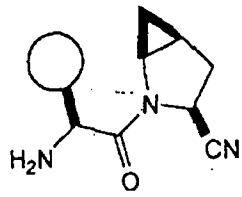
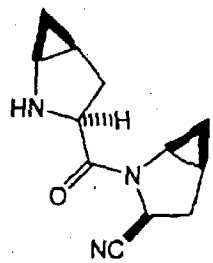
The title compound was prepared from Step 3 compound according to the procedure in General Method C where the amino acid was coupled, the amide was dehydrated, and the protecting group removed to give the title compound. MS (M+H)234.

Examples 86 and 87 were prepared by the procedures used for Example 85 starting from cyclohexanone and cyclobutanone respectively.

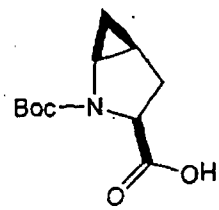


Example #	Cycloalkane	Mass Spec M+H
85	cyclopentyl	234
86	cyclohexyl	248
87	cyclobutyl	220

Example 89



Step 1



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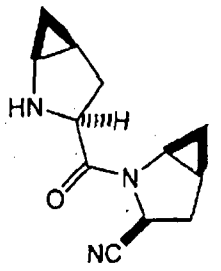
Step 1 compound was prepared in Example 6 Step 1.

Step 2



The title compound was prepared from Step 1 compound according to General Method C, where the carboxylic acid underwent a peptide coupling, the amide dehydration and protecting group removal. MS (M+H) 218.

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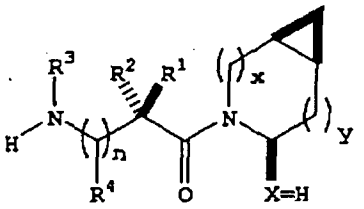
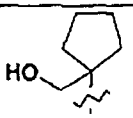
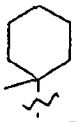
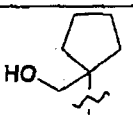
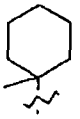
Examples 90 to 99

Examples of compounds where X = H include the following compounds which may be prepared employing procedures as described hereinbefore.



Ex. #	n	x	y	R^1	R^2	R^3	R^4
90	0	0	1	*t*-Bu	H	H	-
91	0	0	1	adamantyl	H	H	-
92	0	0	1		H	H	-
93	0	0	1		H	Me	-
94	0	1	0	*t*-Bu	H	H	-
95	0	1	0	adamantyl	H	H	-
96	0	1	0		H	H	-
97	0	1	0		H	Me	-
98	1	0	1	*H*	*H*	*H*	*t*-Bu
99	1	1	0	Me	H	H	*t*-Bu

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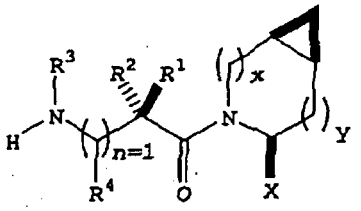
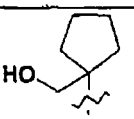
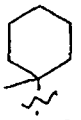
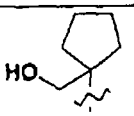
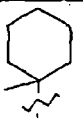
Examples 100 to 109

Examples of compounds where n = 1 include the following compounds which may be prepared employing procedures as described hereinbefore.



Ex. #	X	x	y	R^1	R^2	R^3	R^4
100	CN	0	1	H	H	H	*t*-Bu
101	CN	0	1	H	H	H	adamantyl
102	CN	0	1	H	Me	H	
103	CN	0	1		H	Me	H
104	CN	1	0	*t*-Bu	H	H	H
105	CN	1	0	adamantyl	H	H	Me
106	CN	1	0		Et	H	H
107	CN	1	0	H	H	Me	
108	H	0	1	*t*-Bu	H	H	H
109	H	1	0	Me	H	H	*t*-Bu

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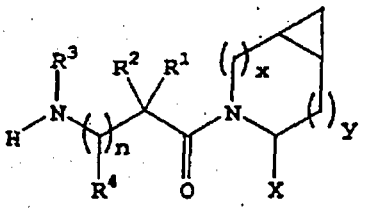
We Claim:

1. A cyclopropyl-fused pyrrolidine-based compound having the structure



wherein x is 0 or 1 and y is 0 or 1, provided that

x = 1 when y = 0 and

x = 0 when y = 1; and wherein

n is 0 or 1;

X is H or CN;

R^1, R^2, R^3 and R^4 are the same or different and are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl, hydroxybicycloalkyl, hydroxytricycloalkyl, bicycloalkylalkyl, alkylthioalkyl, arylalkylthioalkyl, cycloalkenyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl or cycloheteroalkylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3, 4 or 5 groups selected from hydrogen, halo, alkyl, polyhaloalkyl, alkoxy, haloalkoxy, polyhaloalkoxy, alkoxycarbonyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, heteroarylamino, arylamino, cycloheteroalkyl, cycloheteroalkylalkyl, hydroxy, hydroxyalkyl, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, alkylcarbonyl, acyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, alkylsulfonylamino, alkylaminocarbonylamino, alkoxycarbonylamino, alkylsulfonyl, aminosulfinyl, aminosulfonyl, alkylsulfinyl, sulfonamido or sulfonyl;

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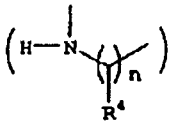
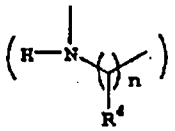
and R^1 and R^3 may optionally be taken together to form $-(CR^5R^6)_m-$ where m is 2 to 6, and R^5 and R^6 are the same or different and are independently selected from hydroxy, alkoxy, H, alkyl, alkenyl, alkynyl, cycloalkyl, halo, amino, substituted amino, cycloalkylalkyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or R^1 and R^4 may optionally be taken together to form $-(CR^7R^8)_p-$ wherein p is 2 to 6, and R^7 and R^8 are the same or different and are independently selected from hydroxy, alkoxy, cyano, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, halo, amino, substituted amino, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, alkoxycarbonyl, aryloxycarbonyl, or alkylaminocarbonylamino, or optionally R^1 and R^3 together with  from a 5 to 7 membered ring containing a total of 2 to 4 heteroatoms selected from N, O, S, SO, or SO_2; or optionally R^1 and R^3 together with  form a 4 to 8 membered cycloheteroalkyl ring wherein the cycloheteroalkyl ring has an optional aryl ring fused thereto or an optional 3 to 7 membered cycloalkyl ring fused thereto;

including all stereoisomers thereof;
and a pharmaceutically acceptable salt thereof, or a prodrug ester thereof, and all stereoisomers thereof.

2. The compound as claimed in claim 1, having the structure:

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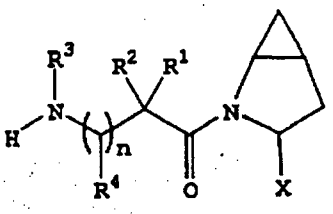
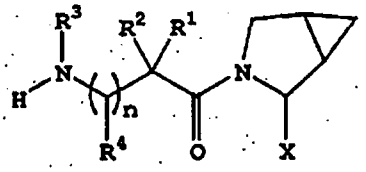
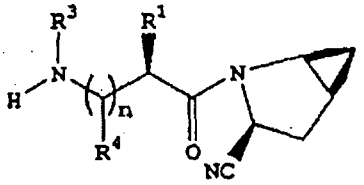


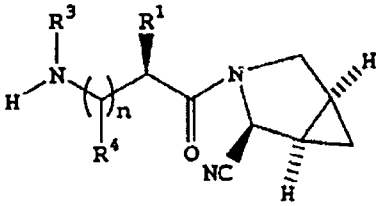
3. The compound as claimed in claim 1, having the structure:



4. The compound as claimed in claim 1, having the structure:



5. The compound as claimed in claim 1, having the structure:



6. The compound as claimed in Claim 1, wherein:

R^3 is H, R^1 is H, alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxyalkylcycloalkyl, hydroxycycloalkyl

hydroxybicycloalkyl, or hydroxytricycloalkyl,

R^2 is H or alkyl, n is 0,

X is CN.

7. The compound as claimed in claim 1, wherein the cyclopropyl fused to the pyrrolidine has the configuration:

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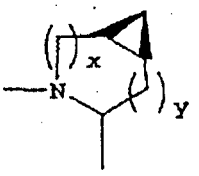
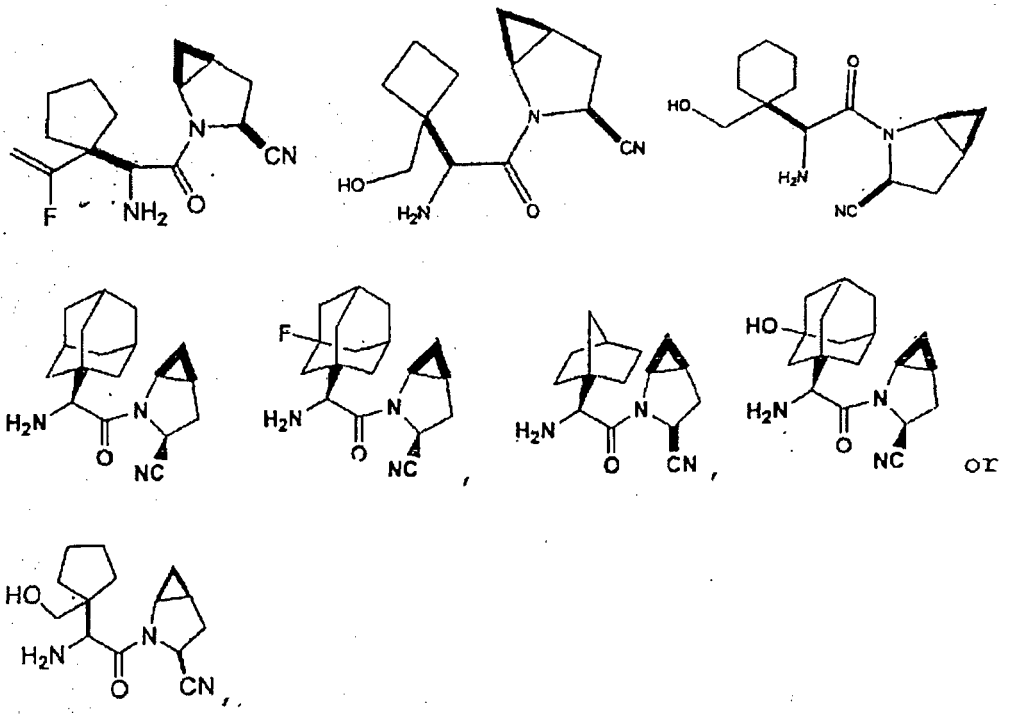
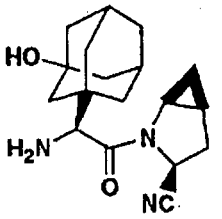


8. The compound as claimed in claim 1, having the structure:



or a pharmaceutically acceptable salt thereof.

9. A compound of formula I as claimed in claim 1-



10. The compound as claimed in claim 8, wherein the pharmaceutically acceptable salt is the hydrochloride salt or the trifluoroacetic acid salt.

11. The compound as claimed in claim 1, which is

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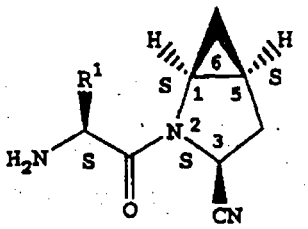
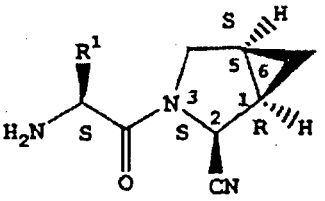


A

(1S,2(2S),3S,5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybicycloalkyl, or hydroxytricycloalkyl, or



B

(1R,2S,3(2S),5S)

wherein R^1 is alkyl, cycloalkyl, bicycloalkyl, tricycloalkyl, alkylcycloalkyl, hydroxyalkyl, hydroxycycloalkyl, hydroxyalkylcycloalkyl, hydroxybiocycloalkyl, or hydroxytricycloalkyl.

12. A pharmaceutical composition comprising a therapeutically effective amount of the compound as claimed in claim 1 and a pharmaceutically acceptable carrier thereof.

13. A pharmaceutical combination comprising a therapeutically effective amount of DP4 inhibitor compound as claimed in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent.

14. The pharmaceutical combination as claimed in claim 13, comprising said DP4 inhibitor compound and an antidiabetic agent.

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15. The combination as claimed in claim 13, wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, an aP2 inhibitor, a glycogen phosphorylase inhibitor, an AGE inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1) or mimetic thereof, insulin and/or a meglitinide.

16. The combination as claimed in claim 14, wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, G1-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, Exendin-4, LY307161, NN2211, and/or LY315902.

17. The combination as claimed in claim 14, wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 100:1.

18. The combination as claimed in claim 13, wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, an anorectic agent, and/or a fatty acid oxidation upregulator.

19. The combination as claimed in claim 18, wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, famoxin, and/or mazindol.

20. The combination as claimed in claim 13, wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase

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inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, an ACAT inhibitor, a cholesteryl ester transfer protein inhibitor, or an ATP citrate lyase inhibitor.

21. The combination as claimed in claim 20, wherein the lipid modulating agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, implitapide, CP-529, 414, avasimibe, TS-962, MD-700, and/or LY295427.

22. The combination as claimed in claim 20, wherein the DP4 inhibitor is present in a weight ratio to the lipid-modulating agent within the range from about 0.01 to about 100:1.

23. A pharmaceutical combination comprising a DP4 inhibitor compound as claimed in claim 1 and an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty, an anti-arthritis agent, an agent for preventing inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent and/or an anti-obesity agent.

Dated this 23rd day of August, 2002.

[DR. DEEPA K. TIKU]
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

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ANNEXURE - B

I, B. KOMBI, of Remfry & Sagar, Attorneys-at-Law, Remfry House, Millennium Plaz Sector 27, Gurgaon 122 002, India do hereby certify that the annexed document is a true cop of the original deed of assignment which was filed by us in the Indian Patent Office, Delhi c March 28, 2014 in respect of Indian Patent Application No. IP. 6986/DELNP/2006

(B. KOMB
OF REMFRY & SAGA

NOTARY
GOVT. OF INDIA

ATTESTED
31-3-2014
ADVOCATE & NOTARY
Distt. Gurgaon, Haryana (INDIA)

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- 3 APR 2014

E-101/13390/2014.

57271

DEED OF ASSIGNMENT

We, BRISTOL-MYERS SQUIBB COMPANY, of P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, United States of America,

[hereinafter referred to as the `Assignors] are the applicant for patents in India in respect of Indian patents and Patent Application numbers identified in the Schedule attached hereto [hereinafter referred to as "the said Schedule"];

AND WHEREAS, ASTRAZENECA AB, of SE-151 85, Sodertalje, Sweden,

[hereinafter referred to as the `Assignees] are desirous of acquiring from the Assignors, their entire right, title and interest in and to the said patent and patent applications referred to in the said schedule and in and to any letters patents that may be granted in respect of said patent applications.

AND WHEREAS the Assignors have agreed to assign to the Assignees their entire right, title and interest in and to said patent and patent applications and in and to any letters patents that may be granted in respect of said patent applications referred in the said schedule;

NOW THEREFORE KNOW YE that for and in consideration of the sum of US$ 10.00 paid by the Assignees to the Assignors, the receipt whereof the Assignors hereby acknowledge, the Assignors assign and transfer and by these presents do assign and transfer unto the Assignees, their successors and assigns their entire right, title and interest in and to the said patent and patent applications and in and to any letters patents granted or that may be granted in India in respect of the said patent applications referred in the said schedule and all and singular the liberties, powers, privileges, advantages and immunities whatever appertaining or belonging thereunto including full power to the assignees to cause their name to be substituted for the Assignors name as applicant for said letters patents in respect of the said applications and to proceed with the said applications for letters patent in their name.

IPO MUMBAI 29-06-2015 16:00

-3 APR 2014

IN WITNESS WHEREOF the Assignors have executed these presents

Lisa B. Swidler

Dated this 24th day of Feb. 2014

Henry Hadad, Vice President and Deputy General Counsel, IP
BRISTOL-MYERS SQUIBB COMPANY

IN WITNESS WHEREOF the Assignees have executed these presents

Dated this day of 2014

Benjamin McDonald, Assistant General Counsel
ASTRAZENECA AB

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31-3-2014
ADVOCATE & NOTARY
Gurgaon, Haryana (INDIA)

NOTARY
R.K. MALIK
GOVT.

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- 3 APR 2014

SCHEDULE

Application No.	Patent No.
6986/DELNP/2006	206543
420/DELNP/2008	244388
5914/DELNP/2006 (259073)	
6560/DELNP/2009	

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- 3 APR 2014

We, BRISTOL-MYERS SQUIBB COMPANY, of P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, United States of America,

[hereinafter referred to as the `Assignors] are the applicant for patents in India in respect of Indian patents and Patent Application numbers identified in the Schedule attached hereto [hereinafter referred to as "the said Schedule"];

AND WHEREAS, ASTRAZENECA AB, of SE-151 85, Sodertalje, Sweden,

[hereinafter referred to as the `Assignees] are desirous of acquiring from the Assignors, their entire right, title and interest in and to the said patent and patent applications referred to in the said schedule and in and to any letters patents that may be granted in respect of said patent applications.

AND WHEREAS the Assignors have agreed to assign to the Assignees their entire right, title and interest in and to said patent and patent applications and in and to any letters patents that may be granted in respect of said patent applications referred in the said schedule;

NOW THEREFORE KNOW YE that for and in consideration of the sum of US$ 10.00 paid by the Assignees to the Assignors, the receipt whereof the Assignors hereby acknowledge, the Assignors assign and transfer and by these presents do assign and transfer unto the Assignees, their successors and assigns their entire right, title and interest in and to the said patent and patent applications and in and to any letters patents granted or that may be granted in India in respect of the said patent applications referred in the said schedule and all and singular the liberties, powers, privileges, advantages and immunities whatever appertaining or belonging thereunto including full power to the assignees to cause their name to be substituted for the Assignors name as applicant for said letters patents in respect of the said applications and to proceed with the said applications for letters patent in their names.

GOVT. OF INDIA

IPO MUMBAI 29-06-2015 16:00

- 3 APR 2014

IN WITNESS WHEREOF the Assignors have executed these presents

Dated this day of 2014

Henry Hadad, Vice President and Deputy General Counsel, IP
BRISTOL-MYERS SQUIBB COMPANY

IN WITNESS WHEREOF the Assignees have executed these presents

Dated this 10th day of February 2014

Benjamin McDonald, Assistant General Counsel
ASTRAZENECA AB

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31-3-2014
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- 3 APR 2014

SCHEDULE

Application No.	Patent No.
6986/DELNP/2006	206543
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- 3 APR 2014

AstraZeneca

14 Tablets

Each film-coated tablet contains:
Saxagliptin hydrochloride equivalent to Saxagliptin 2.5 mg
Colours: Ferric Oxide Yellow USP NF, Indigo Carmine & Titanium Dioxide I.P.

Rx saxagliptin tablets

onglyza® 2.5mg

Dosage: As directed by the physician.
Tablets should be swallowed whole & not chewed or crushed.

Warning: To be sold by retail on prescription of a Registered Medical Practitioner Only

See package insert for indication, dosage & precautions.
Keep out of the reach of Children
Store below 30°C

® Registered Trademark
Onglyza® is a Trademark of AstraZeneca Group of Companies

MANUFACTURED BY
Bristol-Myers Squibb, S.r.l.
Contrada Fontana del Ceraso
03012 Anagni,
Frosinone, Italy

1006958353

Import Licence No: FF-380-27070
B.No. 4J81916
Mfd. 02.2014
Exp. 01.2017

Imported and Marketed By:
Astra Zeneca Pharma India Limited
Sy.No. 5-2/E. 12th Mile on Bellary Road,
Bangalore -560063, India.

Maximum Retail Price ₹ 605
Per blister of 14 Tablets
(Inclusive of all taxes)

For Sale in India and Nepal only

Bristol-Myers Squibb AstraZeneca

14 Tablets

Each film-coated
Saxagliptin hydro
to Saxagliptin 5 m
Colours: Ferric O
Indigo Carmine & Titanium Dioxide I.P.

1004626821

Rx saxagliptin tablets

onglyza® 5mg

Dosage: As directed by the physician.
Tablets should be swallowed whole & not chewed or crushed.

Warning: To be sold by retail on prescription of a Registered Medical Practitioner Only

See package insert for indication, dosage & precautions.
Keep out of the reach of Children
Store below 30°C

Onglyza is a registered trademark of Bristol-Myers Squibb Company.

Marketed by:
Bristol-Myers Squibb India Private Limited,
6th floor, Towers 1 & 2,
Indiabulls Finance Centre,
S.B. Marg, Elphinstone (W),
Mumbai- 400 013, India
And
AstraZeneca Pharma India Ltd
Bangalore -560024, India

MANUFACTURED BY
Bristol-Myers Squibb, S.r.l.
Contrada Fontana del Ceraso
03012 Anagni,
Frosinone, Italy

IMPORTED BY
Bristol-Myers Squibb India Private Limited
Bldg. B4, Gala No. 1 to 4, 5A & 6A
City Link Ware houses complex
Mumbai Nashik Highway, Vadpe Village
Tal: Bhiwandi (Thane-Zone 5)
Pin-421302

Import Licence No: FF-380-16259
B.No. 4A83923
Mfd. 09.2013
Exp. 09.2016

Maximum Retail Price ₹ 581
Per blister of 14 Tablets
(Inclusive of all taxes)

IPO MUMBAI 29-06-2015 16:00

170

℞ 1x7 Tablets

Saxagliptin & Metformin HCl
Extended Release Tablets

kombiglyze™ XR

5mg/1000mg

AstraZeneca

Each Film coated Tablet contains:
Saxagliptin hydrochloride equivalent to Saxagliptin 5mg.
Metformin hydrochloride IP (Extended Release) 1000mg
Colours: Ferric oxide Red US NF, Indigo carmine & Titanium Dioxide I P

B.No. 4H68953A

Mfd. AUG 2014

Exp. JUL 2017

Warning: To be sold by retail on prescription of a Registered Medical Practitioner Only.

Caution: It is dangerous to take this preparation except under medical supervision

Keep out of the reach of Children

Store below 30°C

Dosage: As directed by the Physician

Tablets should be swallowed whole and not chewed or crushed

MANUFACTURED BY
Bristol-Myers Squibb Company
4501 Highway 62 East
Mount Vernon, Indiana 47620, USA

Maximum Retail Price per blister of 7 tablets Not to Exceed ₹343 (Inclusive of all taxes)

Imported and Marketed By:
AstraZeneca Pharma India Limited
Sy.No, 5-2/E, 12th Mile on Bellary Road,
Bangalore -560063, India

Import Licence No: FF-357-27069

Kombiglyze™ is a trademark of AstraZeneca group of companies

℞ 1x7 Tablets

Saxagliptin & Metformin HCl
Extended Release Tablets

kombiglyze™ XR

5mg/500mg

1006889174

Each Film coated Tablet contains:
Saxagliptin hydrochloride equivalent to Saxagliptin 5mg.
Metformin hydrochloride IP (Extended Release) 500mg
Colours: Ferric oxide Yellow US NF, Ferric oxide Red US NF, Indigo carmine & Titanium Dioxide I.P.

B.No. 4K80879A

Mfd. OCT 2014

Exp. SEP 2017

Warning: To be sold by retail on prescription of a Registered Medical Practitioner Only.

Caution: It is dangerous to take this preparation except under medical supervision

Keep out of the reach of Children

Store below 30°C

Dosage: As directed by the Physician

Tablets should be swallowed whole and not chewed or crushed

MANUFACTURED BY
Bristol-Myers Squibb Company
4801 Highway 62 East
Mount Vernon, Indiana 47620, USA

Imported and Marketed By:
AstraZeneca Pharma India Limited
Sy.No, 5-2/E, 12th Mile on Bellary Road,
Bangalore -560063, India

Import Licence No: FF-357-27069

Maximum Retail Price per blister of 7 tablets Not to Exceed ₹343 (Inclusive of all taxes)

Kombiglyze™ is a trademark of AstraZeneca group of companies

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International Diabetes Federation

IDF DIABETES ATLAS Sixth edition

2014 UPDATE

1/12 people with **DIABETES**

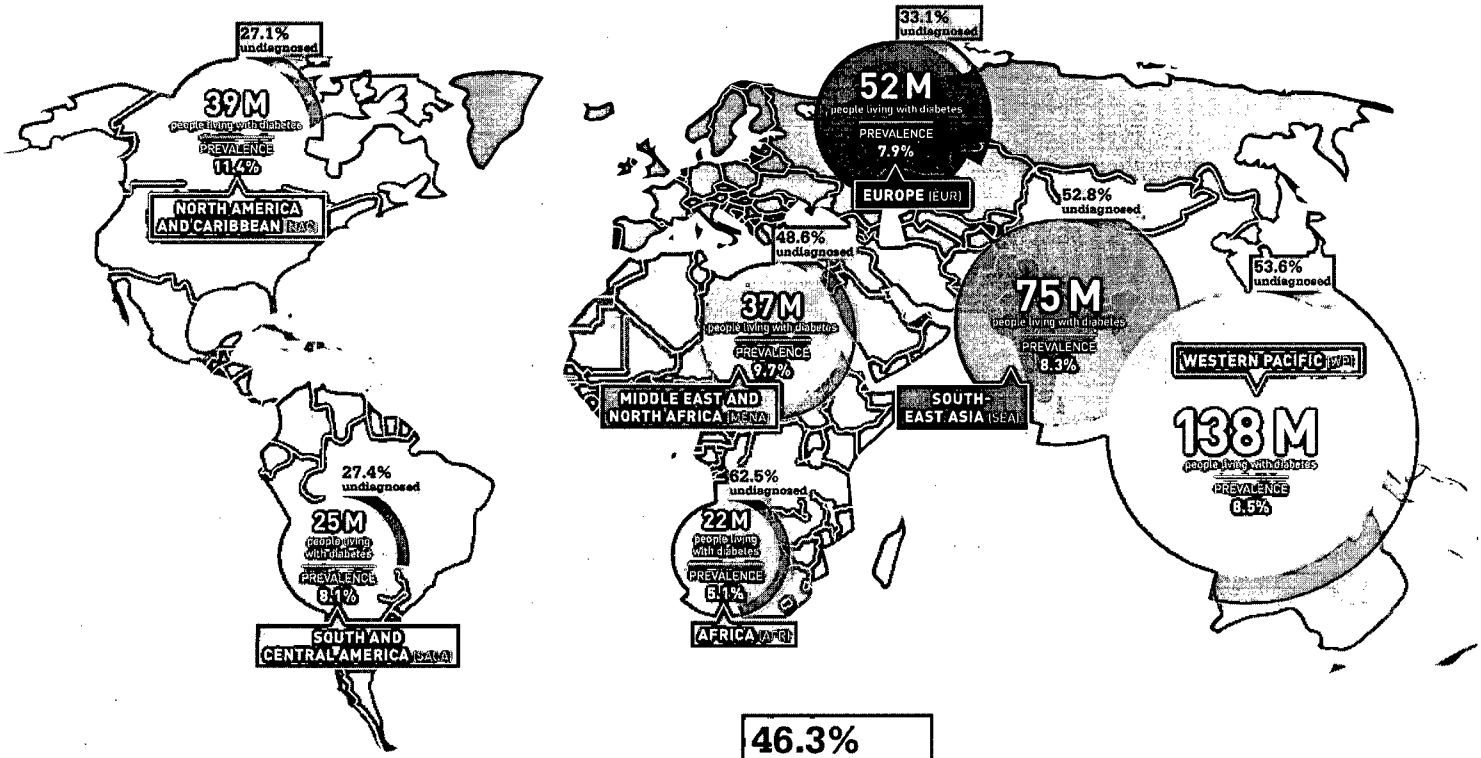
1 in 2 people with diabetes **DO NOT KNOW** they have it

every **7 SECONDS** 1 person dies from diabetes

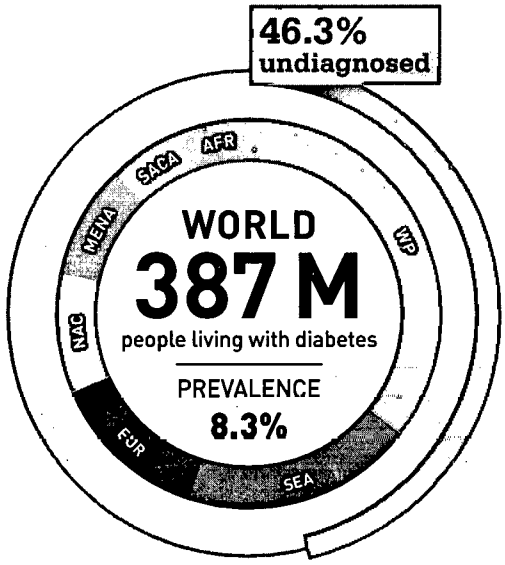
4.9 million deaths in 2014

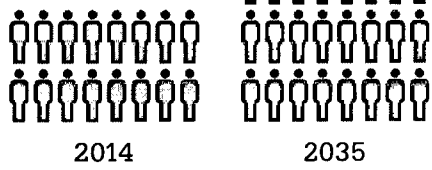
1 healthcare **in 9** **IS SPENT ON DIABETES**

In 2014 diabetes expenditure reached US$612 billion



77% of people with diabetes live in low- and middle-income countries





CORPORATE SPONSORS
IDF would like to express its thanks to the following sponsors for their generous support of this update of the IDF Diabetes Atlas:

Lilly DIABETES · MERCK · novo nordisk Supported through an unrestricted grant by the Novo Nordisk Changing Diabetes® Initiative · Pfizer · SANOFI DIABETES

Want more information?

See **www.idf.org/diabetesatlas** or scan the QR code for the app available for iPad

DIABETES ATLAS

Country summary table: estimates for 2014

COUNTRY/ TERRITORY	Diabetes cases (20-79) in 1000s	Undiagnosed diabetes cases (20-79) in 1000s	Diabetes national prevalence (%)	Diabetes comparative prevalence (%)	Diabetes related deaths (20-79)	Cost/person with diabetes* (USD)
AFRICA	**21,502.92**	**19,443.96**	**5.05**	**5.86**	**480,882.43**	**208.07**
Angola	184.48	84.86	1.99	2.61	4,456.86	390.74
Benin	66.29	49.78	1.34	1.54	1,221.41	64.50
Botswana	30.59	14.07	2.72	3.9	1,118.15	657.69
Burkina Faso	243.18	182.59	3.2	3.72	6,264.55	73.87
Burundi	195.92	147.11	4.17	4.83	4,829.10	38.21
Cabo Verde	15.61	7.18	5.26	5.85	157.30	227.14
Cameroon	515.28	237.03	4.9	5.92	13,821.95	108.87
Central African Republic	150.18	112.76	6.49	7.34	3,933.98	31.15
Chad	264.61	198.68	4.95	5.77	6,925.95	61.17
Comoros	24.51	18.40	6.82	8.38	284.41	65.86
Côte d'Ivoire	490.17	225.48	4.94	5.56	11,883.88	162.43
Democratic Republic of the Congo	2,035.87	1,528.63	6.65	7.56	33,618.92	28.34
Djibouti	28.15	12.95	5.67	6.36	532.56	214.95
Equatorial Guinea	20.49	10.25	5.16	6.13	436.77	2,036.62
Eritrea	149.66	112.37	4.89	5.73	1,719.59	27.52
Ethiopia	2,134.99	1,603.06	4.84	5.47	34,262.16	32.73
Gabon	78.31	36.02	9.05	10.71	1,298.68	637.62
Gambia	12.88	9.67	1.56	1.96	198.03	51.08
Ghana	450.02	337.89	3.34	3.8	8,528.49	148.42
Guinea	218.55	164.10	3.86	4.37	3,964.69	59.19
Guinea-Bissau	27.81	20.88	3.32	3.79	660.15	55.60
Kenya	775.21	582.07	3.6	4.54	15,522.51	81.79
Lesotho	39.80	18.31	3.69	4.5	1,866.80	246.59
Liberia	68.47	51.41	3.34	3.79	1,375.42	123.21
Madagascar	361.01	271.06	3.3	3.73	5,298.43	34.45
Malawi	389.68	292.59	5.32	5.59	12,799.49	46.38
Mali	85.25	64.01	1.29	1.6	1,971.74	86.52
Mauritania	94.89	43.65	4.82	5.22	1,287.55	93.02
Mozambique	286.10	214.82	2.47	2.82	10,103.84	73.44
Namibia	65.96	30.34	5.33	6.86	1,386.41	803.53
Niger	318.19	238.91	4.35	4.18	5,554.96	49.06
Nigeria	3,746.51	1,723.39	4.64	5.27	105,090.67	178.39
Republic of Congo	112.50	51.75	5.26	5.91	2,549.26	183.78
Réunion	96.21	44.26	16.63	15.39	-	-
Rwanda	299.13	224.60	5.45	6.25	5,464.11	123.80
Sao Tome and Principe	4.79	2.20	5.03	5.88	61.72	196.22
Senegal	291.98	134.31	4.4	5.14	3,474.27	95.69
Seychelles	7.84	3.61	12.26	11.98	90.70	661.19
Sierra Leone	97.62	73.30	3.28	3.76	2,890.58	179.65
Somalia	290.68	218.26	6.45	7.29	5,152.57	22.53
South Africa	2,713.38	1,248.16	8.39	9.36	68,977.45	948.54
South Sudan	464.13	213.50	8.43	10.08	8,015.04	-
Swaziland	22.64	10.41	3.55	4.33	1,378.35	473.18
Togo	133.02	99.87	3.99	4.72	2,516.19	73.10
Uganda	693.19	520.48	4.42	5.19	17,570.10	87.74
United Republic of Tanzania	1,794.84	1,347.65	7.95	9.15	36,065.17	75.36
Western Sahara	40.16	30.15	10.46	11.15	-	-
Zambia	266.89	122.77	4.2	5.04	7,599.31	191.30
Zimbabwe	605.12	454.35	8.48	9.34	16,704.11	58.61
EUROPE	**51,978.31**	**17,192.09**	**7.87**	**6.24**	**537,016.07**	**2,775.98**
Albania	64.07	19.42	2.93	2.57	869.60	334.46
Andorra	4.44	1.51	7.44	5.35	31.02	3,524.26
Armenia	58.28	17.67	2.78	2.58	1,026.17	216.20
Austria	573.89	195.15	8.97	6.29	4,335.31	6,137.21
Azerbaijan	156.49	47.45	2.39	2.56	2,395.19	630.62
Belarus	445.96	135.22	6.3	5.07	7,540.95	429.41
Belgium	506.93	172.38	6.33	4.66	4,075.74	5,678.98
Bosnia and Herzegovina	343.24	104.07	12.01	9.6	3,335.80	523.72
Bulgaria	402.79	122.13	7.27	5.04	6,299.21	611.64
Channel Islands	9.04	3.07	7.36	5.39	-	-
Croatia	219.65	74.69	6.86	5.52	2,106.76	1,060.64
Cyprus	87.06	29.61	10.24	9.26	488.10	2,295.60
Czech Republic	729.01	247.90	8.87	6.59	7,264.00	1,669.56
Denmark	337.39	114.73	8.3	6.05	3,098.14	7,505.37
Estonia	73.13	24.87	7.65	5.65	932.17	1,198.29
Faeroe Islands	2.83	0.96	7.77	5.38	-	-
Finland	352.64	119.91	8.9	5.77	2,893.93	4,824.07
France	3,241.34	1,102.22	7.17	5.16	26,182.96	5,600.24
Georgia	97.61	29.60	3.11	2.55	1,542.48	444.01
Germany	7,279.35	2,475.34	11.52	7.93	59,542.78	4,943.62
Greece	585.39	199.06	7.04	4.81	4,735.19	2,354.47
Hungary	565.40	171.43	7.51	5.94	7,383.39	1,158.60
Iceland	9.21	3.13	4	3.2	59.93	5,207.42
Ireland	207.64	70.61	6.41	5.37	1,528.53	4,977.38
Israel	309.12	105.12	6.43	5.46	2,300.33	3,294.68
Italy	3,515.80	1,195.55	7.71	4.93	23,061.94	3,371.23
Kazakhstan	536.40	162.64	4.92	5.01	9,927.87	817.41
Kyrgyzstan	169.59	84.79	5.08	6.3	2,786.09	135.08
Latvia	104.04	35.38	6.74	4.98	1,240.91	954.66
Liechtenstein	2.13	0.73	7.8	5.4	13.41	-
Lithuania	109.48	37.23	4.84	3.82	1,704.33	1,098.05
Luxembourg	22.40	7.62	5.77	4.53	169.78	9,423.69
Malta	35.22	11.98	10.69	7.33	269.39	2,113.78
Moldova (Republic of)	74.69	22.65	2.87	2.52	1,361.85	333.04
Monaco	2.15	0.73	7.69	5.35	14.33	7,711.76
Montenegro	53.83	16.32	12	9.82	636.35	-
Netherlands	886.70	301.52	7.24	5	7,203.56	6,943.11
Norway	249.20	84.74	6.93	5.24	1,657.68	11,144.28
Poland	2,049.06	696.78	7.08	5.63	20,535.28	1,061.83
Portugal	1,042.39	354.47	13.09	9.59	7,994.34	2,011.88
Romania	1,530.25	463.97	9.28	7.99	17,285.55	490.64
Russian Federation	6,762.51	2,299.59	6.23	5.03	123,483.18	1,120.69
San Marino	1.75	0.60	7.43	5.35	12.21	4,370.14
Serbia	844.08	255.92	11.96	9.75	9,965.88	666.93
Slovakia	387.26	131.69	9.28	7.21	4,892.20	1,633.93
Slovenia	158.81	54.00	10.03	7.17	1,433.85	2,183.93
Spain	3,704.07	1,259.57	10.58	7.85	24,427.96	3,090.59
Sweden	426.80	145.13	6.14	4.51	2,929.02	6,308.58
Switzerland	438.05	148.96	7.18	5.63	2,486.90	10,592.28
Tajikistan	202.82	101.41	4.54	6.44	2,617.81	96.09
TFYR Macedonia	180.18	54.63	11.44	9.76	1,914.24	403.05
Turkey	7,227.45	2,191.36	14.71	14.84	59,755.22	895.00
Turkmenistan	133.87	40.59	4.08	5.01	2,540.03	219.53
Ukraine	1,099.86	333.48	3.17	2.58	20,486.38	377.12
United Kingdom	2,452.83	834.09	5.38	3.9	21,406.14	4,466.07
Uzbekistan	912.73	276.74	5.1	6.43	12,834.68	166.09
MIDDLE EAST AND N. AFRICA	**36,790.84**	**17,862.20**	**9.72**	**11.26**	**362,819.53**	**457.89**
Afghanistan	805.22	402.61	6.15	8.07	18,513.73	101.75
Algeria	1,649.07	824.54	6.54	7.29	14,043.57	422.87
Bahrain	170.57	69.42	17.53	21.87	820.11	1,195.52
Egypt	7,593.27	3,796.64	15.42	16.56	72,371.82	213.20
Iran (Islamic Republic of)	4,581.61	2,290.80	8.64	10.01	38,078.83	721.97
Iraq	1,291.21	645.61	7.55	9.6	17,773.35	399.90
Jordan	378.26	189.13	8.89	11.45	3,111.45	638.74
Kuwait	424.04	172.59	17.87	23.13	1,232.25	1,949.05
Lebanon	494.29	247.14	14.36	14.92	6,358.10	834.29
Libya	326.82	163.41	8.54	9.79	2,701.96	908.04
Morocco	1,552.17	776.08	7.45	7.88	9,517.58	289.25
Oman	220.64	89.80	8.16	14.49	1,220.17	1,068.50
Pakistan	6,943.79	3,471.89	6.8	7.93	87,547.56	55.75
Qatar	303.72	123.62	16.28	19.78	643.37	2,748.23
Saudi Arabia	3,806.37	1,549.19	20.52	23.9	25,526.76	1,067.32
State of Palestine	140.87	70.43	6.58	9.16	-	-
Sudan	3,007.55	1,503.78	16.15	17.91	39,226.63	180.86
Syrian Arab Republic	875.71	437.85	7.4	8.79	8,013.46	181.16
Tunisia	704.35	352.18	9.33	9.41	5,122.80	418.55
United Arab Emirates	803.94	327.20	10.68	19.02	1,335.08	1,967.44
Yemen	716.57	358.28	5.96	8.25	9,660.95	131.29
NORTH AMERICA AND CARIBBEAN	**38,832.42**	**10,511.54**	**11.45**	**9.2**	**237,223.38**	**7,983.79**
Anguilla	1.22	0.30	13.15	12.62	-	-
Antigua and Barbuda	7.94	2.20	13.43	13.08	94.99	927.62
Aruba	12.08	3.35	16.24	13.03	-	-
Bahamas	34.87	9.66	13.14	12.84	344.94	2,180.91
Barbados	30.53	8.46	14.78	12.35	269.98	1,141.45
Belize	25.47	6.37	13.52	15.88	261.53	404.45
Bermuda	6.90	1.91	14.94	12.77	-	-
British Virgin Islands	2.37	0.59	12.96	12.62	-	-
Canada	3,033.63	840.62	11.62	9.41	17,923.48	6,741.48
Cayman Islands	5.02	1.39	13.24	12.77	-	-
Curaçao	18.23	5.05	15.9	12.82	-	-
Dominica	5.31	1.33	11.47	10.99	47.72	543.35
Grenada	5.55	1.39	8.39	9.22	81.87	718.23
Guadeloupe	25.18	6.29	7.94	6.33	-	-
Guyana	61.76	15.44	14.26	15.84	1,025.30	372.02
Haiti	318.26	93.57	5.61	6.7	6,313.72	91.06
Jamaica	183.82	45.96	10.76	10.53	1,828.49	460.98
Martinique	45.67	12.65	16.08	12.82	-	-
Mexico	9,018.62	2,254.65	11.92	12.63	68,659.76	892.53
Montserrat	0.45	0.12	13.74	13.06	-	-
Saint Kitts and Nevis	4.64	1.28	13.21	12.55	58.67	1,120.91
Saint Lucia	10.23	2.56	8.51	8.31	93.24	794.52
Saint Vincent and the Grenadines	6.99	1.75	9.91	9.95	87.10	493.92
Sint Maarten (Dutch part)	3.90	1.08	13.23	12.77	-	-
Suriname	36.74	9.19	10.74	10.83	463.08	762.50
Trinidad and Tobago	135.59	37.57	14.17	13.09	1,461.09	1,238.60
United States of America	25,779.34	7,143.46	11.39	9.39	198,208.37	10,902.17
United States Virgin Islands	12.10	3.35	16.24	12.1	-	-
SOUTH AND CENTRAL AMERICA	**26,723.30**	**6,727.49**	**9.11**	**9.18**	**219,050.38**	**1,599.64**
Argentina	1,626.07	451.72	5.97	5.65	15,220.51	1,422.73
Bolivia (Plurinational State of)	371.09	103.09	6.3	7.28	4,694.31	252.08
Brazil	11,623.32	3,228.96	8.68	8.7	116,382.56	1,527.57
Chile	1,513.41	325.53	12.32	11.19	8,956.43	1,427.04
Colombia	2,191.92	608.92	7.17	7.26	14,168.18	805.03
Costa Rica	305.73	84.93	9.27	9.5	1,590.15	1,364.45
Cuba	702.39	195.12	8.37	6.7	5,920.69	704.68
Dominican Republic	669.86	186.09	10.74	11.35	7,888.33	466.05
Ecuador	544.39	151.23	5.71	5.91	4,540.90	562.53
El Salvador	386.79	107.45	10.55	11.75	3,675.70	377.29
French Guiana	12.11	3.37	8.16	8.54	-	-
Guatemala	679.99	188.90	8.93	10.84	7,964.67	385.38
Honduras	420.78	116.89	9.53	11.69	2,774.20	319.71
Nicaragua	356.10	98.92	10.32	12.45	3,166.62	221.27
Panama	202.16	56.16	8.36	8.54	1,396.92	1,096.20
Paraguay	243.78	67.72	6.2	7	2,242.00	658.24
Peru	1,143.59	317.69	6.1	6.54	7,650.27	523.53
Puerto Rico	397.13	110.05	15.5	12.98	-	-
Uruguay	150.26	32.32	6.58	5.76	1,040.09	1,742.08
Venezuela (Bolivarian Republic of)	1,252.44	347.93	6.58	6.86	9,777.78	935.45
SOUTH-EAST ASIA	**74,957.00**	**39,581.63**	**8.33**	**8.83**	**1,185,208.36**	**92.17**
Bangladesh	5,982.18	2,979.12	6.34	6.89	111,371.48	42.59
Bhutan	23.39	12.42	4.94	5.83	124.36	149.99
India	66,846.88	35,495.69	8.63	9.11	1,039,980.44	94.96
Maldives	17.05	9.05	7.97	9.41	108.51	869.63
Mauritius	209.71	111.36	23.5	21.15	2,460.75	485.03
Nepal	700.74	348.97	4.58	4.96	14,778.47	60.00
Sri Lanka	1,177.05	625.01	8.32	7.8	16,384.35	122.57
WESTERN PACIFIC	**137,818.47**	**74,837.24**	**8.45**	**7.89**	**1,021,476.24**	**732.91**
Australia	859.19	463.53	5.14	4.08	4,962.91	7,931.05
Brunei Darussalam	21.57	11.64	7.69	8.03	224.87	1,384.01
Cambodia	229.42	144.63	2.56	2.96	5,534.27	88.13
China	96,288.03	51,273.38	9.32	8.64	1,205,922.56	421.32
Cook Islands	3.12	1.68	25.44	25.54	11.34	637.94
Dem. People's Republic of Korea	1,163.48	733.46	6.68	6.15	27,890.18	-
Fiji	58.77	31.30	10.71	10.88	1,053.34	263.29
French Polynesia	47.16	25.44	24.83	24.42	-	-
Guam	22.61	12.20	21.13	20.05	-	-
Hong Kong SAR (China)	568.38	306.64	9.92	7.66	-	1,811.37
Indonesia	9,116.03	4,854.29	5.81	6.03	175,936.01	174.71
Japan	7,212.05	3,890.90	7.6	5.12	64,714.52	4,908.07
Kiribati	14.22	7.57	23.89	26.43	145.15	246.04
Lao People's Democratic Republic	149.28	94.11	4.06	5.03	3,709.74	74.24
Macao SAR (China)	43.08	23.24	9.33	8.63	-	1,026.77
Malaysia	3,225.17	1,717.40	16.61	17.64	34,421.92	565.35
Marshall Islands	11.85	6.31	37.37	37.06	229.16	654.27
Micronesia (Fed. States of)	16.64	8.86	30.75	36.3	170.35	516.00
Mongolia	133.75	71.22	7.27	7.5	2,961.76	336.88
Myanmar	2,050.98	1,292.94	5.79	6.14	60,517.69	30.87
Nauru	1.42	0.76	23.47	23.27	21.71	722.50
New Caledonia	37.61	20.29	21.34	20.06	-	-
New Zealand	384.32	207.34	12.14	9.9	2,326.36	3,883.23
Niue	0.10	0.05	13.11	13.4	0.75	1,819.96
Palau	2.38	1.27	18.72	18.46	27.12	1,289.47
Papua New Guinea	200.94	107.00	5.22	6.33	4,932.38	209.04
Philippines	3,273.59	1,743.18	5.89	6.71	53,548.95	205.50
Republic of Korea	2,767.69	1,493.17	7.33	5.97	27,804.63	2,144.39
Samoa	6.98	3.72	7.16	7.64	160.80	429.32
Singapore	533.63	287.89	12.83	10.79	4,246.69	2,858.02
Solomon Islands	37.93	20.20	13.51	16.12	495.33	236.73
Taiwan	1,757.05	947.93	9.92	8.3	-	1,219.33
Thailand	4,175.55	2,223.48	8.45	7.36	84,347.71	285.43
Timor-Leste	26.20	13.95	5.6	6.76	589.60	105.23
Tokelau	0.22	0.12	29.81	29.64	-	-
Tonga	7.41	3.95	13.79	14.76	110.49	360.78
Tuvalu	0.90	0.48	15.35	15.33	15.73	801.34
Vanuatu	28.63	15.24	21	23.71	356.47	165.06
Viet Nam	3,336.12	1,776.49	5.33	5.71	54,105.77	149.89
WORLD	**386,667.28**	**179,211.69**	**8.33**	**8.19**	**4,903,698.14**	**1,583.31**

*mean diabetes-related healthcare expenditure per person with diabetes, given in US dollars

DEFINITIONS

Prevalence is the proportion of individuals in a population which has a disease or condition at a particular time (be it a point in time or time period).

Comparative prevalence is calculated by assuming that every country and region has the same age profile that is identical to the age profile of the world population. Comparative prevalence should be used for comparing countries and regions, and should not be used for assessing the true proportion of people who have diabetes within a country or region.

National or regional prevalence indicates the actual percentage of each country's or region's population that has diabetes. It is appropriate for assessing the burden of diabetes for each country or region, but not comparing between countries or regions with different age structures.

All reported figures refer to the adult population aged 20-79.

Want more information?

See **www.idf.org/diabetesatlas** or scan the QR code for the app available for iPad

FCAT FILE (WHO)
http://www.who.int/features/factfiles/diabetes/facts/en/

10 FACTS ABOUT DIABETES

1. About 347 million people worldwide have diabetes

There is an emerging global epidemic of diabetes that can be traced back to rapid increases in overweight, including obesity and physical inactivity.

2. Diabetes is predicted to become the 7th leading cause of death in the world by the year 2030

Total deaths from diabetes are projected to rise by more than 50% in the next 10 years.

3. There are two major forms of diabetes

Type 1 diabetes is characterized by a lack of insulin production and type 2 diabetes results from the body's ineffective use of insulin.

4. A third type of diabetes is gestational diabetes

This type is characterized by hyperglycaemia, or raised blood sugar, with values above normal but below those diagnostic of diabetes, occurring during pregnancy. Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. They are also at increased risk of type 2 diabetes in the future.

5. Type 2 diabetes is much more common than type 1 diabetes

Type 2 accounts for around 90% of all diabetes worldwide. Reports of type 2 diabetes in children – previously rare – have increased worldwide. In some countries, it accounts for almost half of newly diagnosed cases in children and adolescents.

6. Cardiovascular disease is responsible for between 50% and 80% of deaths in people with diabetes

Diabetes has become one of the major causes of premature illness and death in most countries, mainly through the increased risk of cardiovascular disease (CVD).

7. In 2012 diabetes was the direct cause of 1.5 million deaths

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FCAT FILE (WHO)
http://www.who.int/features/factfiles/diabetes/facts/en/

8. 80% of diabetes deaths occur in low- and middle-income countries

In developed countries most people with diabetes are above the age of retirement, whereas in developing countries those most frequently affected are aged between 35 and 64.

9. Diabetes is a leading cause of blindness, amputation and kidney failure

Lack of awareness about diabetes, combined with insufficient access to health services and essential medicines, can lead to complications such as blindness, amputation and kidney failure.

10. Type 2 diabetes can be prevented

Thirty minutes of moderate-intensity physical activity on most days and a healthy diet can drastically reduce the risk of developing type 2 diabetes. Type 1 diabetes cannot be prevented.

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ANNEXURE-F

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SHORT COMMUNICATION

Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study

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Abstract
Aims/hypothesis This study reports the results of the first phase of a national study to determine the prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in India.
Methods A total of 363 primary sampling units (188 urban, 175 rural), in three states (Tamilnadu, Maharashtra and Jharkhand) and one union territory (Chandigarh) of India were sampled using a stratified multistage sampling design to survey individuals aged ≥20 years. The prevalence rates of diabetes and prediabetes were assessed by measurement of fasting and 2 h post glucose load capillary blood glucose.
Results Of the 16,607 individuals selected for the study, 14,277 (86%) participated, of whom 13,055 gave blood samples. The weighted prevalence of diabetes (both known and newly diagnosed) was 10.4% in Tamilnadu, 8.4% in Maharashtra, 5.3% in Jharkhand, and 13.6% in Chandigarh. The prevalences of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) were 8.3%, 12.8%, 8.1% and 14.6% respectively. Multiple logistic regression analysis showed that age, male sex, family history of diabetes, urban residence, abdominal obesity, generalised obesity, hypertension and income status were significantly associated with diabetes. Significant risk factors for prediabetes were age, family history of diabetes, abdominal obesity, hypertension and income status.

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Conclusions/interpretations We estimate that, in 2011, Maharashtra will have 6 million individuals with diabetes and 9.2 million with prediabetes, Tamilnadu will have 4.8 million with diabetes and 3.9 million with prediabetes, Jharkhand will have 0.96 million with diabetes and 1.5 million with prediabetes, and Chandigarh will have 0.12 million with diabetes and 0.13 million with prediabetes. Projections for the whole of India would be 62.4 million people with diabetes and 77.2 million people with prediabetes.

Keywords Asian Indians · Diabetes · ICMR · India · INDIAB · Prediabetes · Prevalence · Rural · South Asians · Urban

Abbreviations

CBG	Capillary blood glucose
CEB	Census enumeration block
ICMR–INDIAB	Indian Council of Medical Research–INdia DIABetes
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
PPS	Proportional to population size
PSU	Primary sampling unit
UT	Union territory

Introduction

According to the Diabetes Atlas 2009, India has 51 million people with diabetes. However, this figure is based on a few regional studies. To date, there has been no nationwide study of diabetes in India. The Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study was initiated, in a phased manner, to estimate the prevalence of diabetes in India. This paper presents the results of phase I of this study, involving three states and one union territory (UT), overall representing a population of 213.5 million people (18.1% of India's population).

Methods

The ICMR–INDIAB study methodology has been published separately [1]. This is a cross-sectional survey involving adults aged ≥20 years. The results of Phase I, conducted from November 2008 to April 2010, which includes three states randomly selected to represent the south (Tamilnadu), west (Maharashtra) and east (Jharkhand) of India and one UT representing northern India (Chandigarh) are presented here.

Using a precision of 20% (80% power) and allowing for a non-response rate of 20%, the sample size was calculated to be 4,000 per state (2,800 rural and 1,200 urban) [1], thus 16,000 for Phase I. A stratified multistage sampling design was followed [2]. The primary sampling units (PSUs) were villages in rural areas and census enumeration blocks (CEBs) in urban areas. A three-level stratification was done. A total of 16,607 individuals (5,112 urban and 11,495 rural) were selected from 363 PSUs (188 urban and 175 rural).

Institutional Ethics Committee approval and written informed consent were obtained in the local language.

Data collection

An interviewer-administered questionnaire was used and weight, height, waist and blood pressure measured using standardised techniques.

Fasting capillary blood glucose (CBG) was determined using a One Touch Ultra glucose meter (Johnson & Johnson, Milpitas, CA, USA). Oral glucose (82.5 g, equivalent to 75 g of anhydrous glucose) was given and a 2 h post load CBG was collected. In individuals with self-reported diabetes, only fasting CBG was measured.

Definitions

Diabetes was defined as individuals diagnosed by a physician and on glucose-lowering medications (self-reported) and/or those who had a fasting CBG ≥7 mmol/l (≥126 mg/dl) and/or a 2 h post glucose CBG value ≥12.2 mmol/l (≥220 mg/dl) [3]. Impaired

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fasting glucose (IFG) was defined as a fasting CBG ≥6.1 mmol/l (≥110 mg/dl) and <7 mmol/l (<126 mg/dl) and a 2 h post-glucose value <8.9 mmol/l (<160 mg/dl) [3]. Impaired glucose tolerance (IGT) was defined as a 2 h post glucose CBG ≥8.9 mmol/l (≥160 mg/dl) but <12.2 mmol/l (<220 mg/dl) and a fasting value <7 mmol/l (<126 mg/dl) [3]. Prediabetes was defined as individuals with IFG or IGT or both.

Statistical analysis

Statistical analyses were performed using SAS statistical package (version 9.0; SAS Institute, Inc., Cary, NC, USA). For all stratification, the 2001 Census of India was used. The study population was weighted for calculating prevalence rates. Weights were derived considering the design weight (reciprocal of the probability of selection) and individual response rate. The sampling weights were further normalised at the state/UT level to obtain standard state weights. The final weights were used to produce estimates of population variables. For state projections, Government of India population projections for 2011 were used [4]. For national estimates, the weighted prevalence of three states was used (the UT was excluded as it may inflate projections).

Estimates are expressed as mean ± standard deviation or proportions. To compare continuous variables, Student's t tests were used, whereas χ^2 tests were used to test differences in proportions. Multiple logistic regression analysis was used to examine the association between various exposures and outcomes. Using backward selection, variables that remained significant were retained in the final model. A p value<0.05 was considered significant.

Results

Of the 16,607 individuals selected for the study, 14,277 (86%) participated, of whom 13,055 gave blood samples. There were no significant differences in demographic characteristics between the 'responders' and 'non-responders' (results not shown). The mean (SD) age was 40±14 years, mean literacy rate 68.2% and mean monthly income 4,603 rupees (102 USD). Urban residents had significantly higher BMI, waist circumference, and systolic and diastolic blood pressures in all states after adjustment for age and sex.

Table 1 shows that the overall weighted prevalence of diabetes was 10.4% in Tamilnadu, 8.4% in Maharashtra, 5.3% in Jharkhand and 13.6% in Chandigarh. The ratio of newly diagnosed to known diabetes was more than 1:1 in all areas, except Tamilnadu. The overall weighted prevalences of prediabetes in Tamilnadu, Maharashtra, Jharkhand and Chandigarh were 8.3%, 12.8%, 8.1% and 14.6% respectively. This translates to 4.8 million individuals with diabetes and 3.9 million with prediabetes in Tamilnadu. In Maharashtra, an estimated 6.0 million have diabetes and 9.2 million prediabetes. Jharkhand would have 0.96 million people with diabetes and 1.5 million with prediabetes, and Chandigarh 0.12 million with diabetes and 0.13 million with prediabetes. Out of 211.6 million people who reside in the three states studied, an estimated 137 million are adults, 11.8 million of whom have diabetes and 14.6 million have prediabetes. Extrapolated to the whole country, these estimates would translate to 62.4 million individuals with diabetes and 77.2 million with prediabetes in India.

Figure 1 presents the age- and sex-specific weighted prevalence of diabetes. In all states, the take-off point in prevalence was at 25–34 years with a decline after age 65. At every age interval, the prevalence of diabetes in urban areas was higher compared with rural areas.

Multivariable regression analyses showed that age (OR 1.7 [95% CI 1.6,1.8, p<0.001]), male sex (OR 1.3, [95% CI 1.1,1.5, p<0.001]), family history of diabetes (OR 2.1, [95% CI 1.7,2.6, p<0.001]), urban residence (OR 1.3, [95% CI 1.1,1.5, p=0.001]), abdominal obesity (OR 2.4, [95% CI 2.0,3.0, p<0.001]), generalised obesity (OR 1.6 [95% CI 1.3,2.0, p<0.001]), hypertension (OR 1.5 [95% CI 1.3,1.8, p<0.001]) and income status (OR 1.3 [95% CI 1.2, 1.4, p<0.001]) were significantly associated with diabetes. For prediabetes, age (OR 1.2 [95% CI 1.1,1.3, p<0.001]), family history of diabetes (OR 1.2 [95% CI 1.0,1.5, p=0.045]), abdominal obesity (OR 1.7 [95% CI 1.4,1.9, p<0.001]), hypertension (OR 1.3 [95% CI 1.1,1.5, p=0.005]) and income status (OR 1.2 [95% CI 1.1,1.3, p<0.001]) were significant risk factors.

Discussion

This study is the first from India to estimate prevalence of diabetes and prediabetes, surveying rural and urban inhabitants across selected states of India. The sheer size of the populations of these states contributes to the impact of these findings. Maharashtra has a population of 112.7 million (the size of UK and Italy combined), Tamilnadu 67.4 million (the size of France) and Jharkhand 31.4 million (the size of Canada).

There have only been three multicentre studies on the prevalence of diabetes in India. The earliest study reported a prevalence of 2.1% in urban and 1.5% in rural areas [5]. The National Urban Diabetes Survey [6] showed an overall age-standardised prevalence of 12.1% for diabetes and 14% for IGT in six large metropolitan cities. The Prevalence of Diabetes in India Study [7] reported diabetes prevalence of 5.9% and 2.7% in small towns and rural areas respectively.

In our study, Chandigarh was found to have the highest prevalence of diabetes (13.6%), which is not unexpected as

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Table 1 Weighted prevalence of diabetes and prediabetes in the study population (n=13,055)

Status	Tamilnadu			Maharashtra			Jharkhand			Chandigarh[a]		
	Urban	Rural	Overall	Urban	Rural	Overall	Urban	Rural	Overall	Urban	Rural	Overall
N	1029	2480	3509	1093	2476	3569	840	2051	2891	839	2247	3086
KD (%)	8.5[b]	4.1	6.0	3.7[b]	1.7	2.5	8.4[b]	0.7	2.4	6.6[b]	3.1	6.2
(95% CI)	(7.1, 9.9)	(3.2, 5.0)	(5.2, 6.8)	(2.7, 4.7)	(1.2, 2.3)	(2.0, 3.0)	(6.3, 10.5)	(0.3, 1.0)	(1.8, 3.0)	(5.7, 7.5)	(1.2, 5.0)	(5.4, 7.1)
NDD (%)	5.2[b]	3.8	4.4	7.2[b]	4.9	5.9	5.1[b]	2.3	2.9	7.6	5.2	7.4
(95% CI)	(4.1, 6.3)	(3.0, 4.7)	(3.7, 5.1)	(6.0, 8.5)	(3.9, 5.8)	(5.1, 6.7)	(3.4, 6.8)	(1.7, 2.9)	(2.3, 3.5)	(6.6, 8.6)	(2.8, 7.7)	(6.5, 8.3)
Ratio of KD:NDD	1:0.6	1:0.9	1:0.7	1:1.9	1:2.9	1:2.4	1:0.6	1:3.3	1:1.2	1:1.2	1:1.7	1:1.2
Total diabetes (%)	13.7[b]	7.8	10.4	10.9[b]	6.5	8.4	13.5[b]	3.0	5.3	14.2[b]	8.3	13.6
(95% CI)	(12.3, 15.7)	(6.6, 9.0)	(9.0, 1.0)	(9.4, 12.6)	(5.4, 7.6)	(7.5, 9.3)	(11.3, 16.7)	(2.3, 3.7)	(4.5, 6.1)	(12.7, 15.3)	(5.3, 14.4)	(12.8, 15.2)
IFG (%)	4.8	4.4	4.6	8.7	7.6	8.0	5.3	4.7	4.8	9.3	10.9	9.5
(95% CI)	(3.7, 5.9)	(3.5, 5.3)	(3.9, 5.3)	(7.3, 10.1)	(6.5, 8.8)	(7.1, 8.9)	(3.6, 7.0)	(3.8, 5.6)	(4.0, 5.6)	(8.2, 10.4)	(7.6, 14.4)	(8.5, 10.5)
IGT (%)	3.9[b]	2.2	2.9	3.9[b]	2.6	3.1	4.3[b]	2.2	2.7	3.9	2.5	3.8
(95% CI)	(2.9, 4.9)	(1.6, 2.9)	(2.3, 3.5)	(2.9, 4.9)	(1.9, 3.3)	(2.5, 3.7)	(2.7, 5.9)	(1.6, 2.8)	(2.1, 3.3)	(3.2, 4.6)	(0.8, 4.2)	(3.1, 4.5)
IFG+IGT (%)	1.1	0.6	0.8	2.6[b]	0.9	1.6	1.1	0.5	0.6	1.3	1.3	1.3
(95% CI)	(0.6, 1.6)	(0.3, 1.0)	(0.5, 1.1)	(1.8, 3.4)	(0.5, 1.3)	(1.2, 2.0)	(0.3, 1.9)	(0.2, 0.8)	(0.3, 0.9)	(0.9, 1.7)	(0.1, 2.1)	(0.9, 1.7)
Prediabetes (%)	9.8[b]	7.1	8.3	15.2[b]	11.1	12.8	10.7[b]	7.4	8.1	14.5	14.7	14.6
(95% CI)	(8.3, 11.3)	(6.0, 8.2)	(7.4, 9.2)	(13.2, 7.0)	(9.7, 12.4)	(12.0, 14.1)	(8.6, 13.4)	(6.3, 8.5)	(7.1, 9.1)	(12.7, 15.3)	(11.1, 19.0)	(13.7, 16.3)

NDD, newly detected diabetes; KD, known diabetes; Diabetes, known diabetes and newly diagnosed diabetes

[a] Union territory

[b] $p<0.05$ compared with rural population

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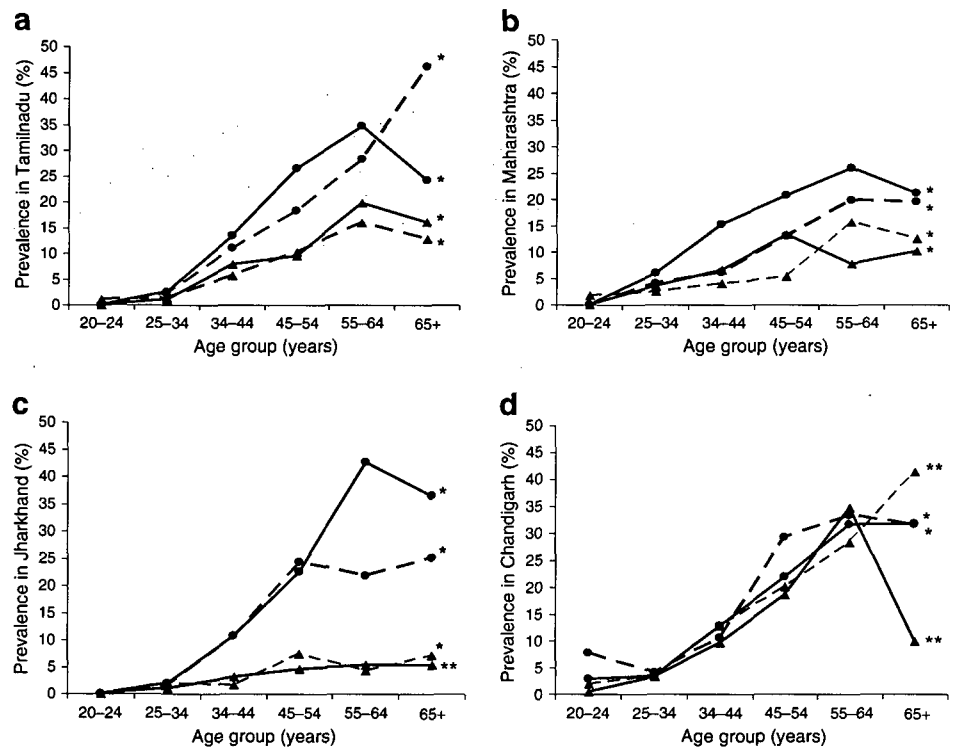

Fig. 1 Age- and sex-specific weighted prevalence of diabetes in the study population. Urban man, circles, solid line; urban woman, circles, dotted line; rural man, triangles, solid line; rural woman, triangles, dotted line. The p value is the p for trend across age groups in the same population; *$p<0.001$, **$p<0.05$

Chandigarh serves as the joint capital of Punjab and Haryana, two prosperous states in India. A previous study reported 11% prevalence in urban Chandigarh [8].

In all four states studied, the prevalence of diabetes was higher in urban, compared with rural areas. This difference was most marked in Jharkhand, where rural–urban disparities in socioeconomic status are among the highest in India. The decrease in prevalence of diabetes after 65 years is possibly due to survivor bias, possibly reflecting deaths at earlier ages due to complications of diabetes. This has significance in planning health services.

The ratio of known to newly diagnosed diabetes is a good indicator of the level of diabetes awareness in a population. In all states studied, the newly detected diabetes cases outnumbered individuals with known diabetes, except in Tamilnadu where periodic screening is done.

The prevalence of prediabetes was higher than that of diabetes in all states except Tamilnadu; the latter is probably due to quicker progression to diabetes [9] or due to ethnic differences. This calls for studies on ethnic differences between states with different risk profiles. The high prevalence of prediabetes is worrisome as this implies a huge population at risk of developing diabetes in the near future.

One of the limitations of this study is the use of CBG, which has a wider coefficient of variation than venous plasma. However, the logistical constraints of insufficient phlebotomists, poor compliance, limited availability of quality-controlled laboratories, and challenges in transporting and storing blood samples precluded the use of venous sampling. Moreover, we have shown good correlation between CBG and venous plasma estimations [10]. Also, although data from three states was used to project the number of people with diabetes in India, and final estimates may vary once the entire study is completed, the sampling frame has ensured representativeness, enhancing the credibility of our estimates.

In conclusion, this study shows that the prevalence of diabetes and prediabetes are higher in both urban and rural areas of India compared with earlier studies. With greater urbanisation, growth of the middle class and ageing of the population, we can expect huge increases in the numbers of people with diabetes in India in the future.

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Contribution statement RMA and VM conceived the study, its design, and were involved in implementation of the study, interpretation of the data and helped to draft and revise the manuscript. RP, MDe, MDa, VS and RU were involved in the design and coordination of the study, interpretation of the data and drafting the manuscript. MKA participated in designing the study and providing critical revision of the manuscript. AB, SRJ, PPJ, CSY and VKD were responsible for supervision of the study in their respective states and were involved in the conception and design of the study. LMN, AKD, PVR, SVM, DKS and TK were part of the study expert committee and helped with the conception and design. MP, EN and SJP helped in the execution of the study, responsible for maintaining quality in the study and analysis and interpretation of data. SS and RS were responsible for data management and statistical analyses. All authors revised the manuscript critically and approved the final manuscript.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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MAYO CLINIC

Diseases and Conditions

Type 2 diabetes

By Mayo Clinic Staff

Type 2 diabetes, once known as adult-onset or noninsulin-dependent diabetes, is a chronic condition that affects the way your body metabolizes sugar (glucose), your body's important source of fuel.

With type 2 diabetes, your body either resists the effects of insulin — a hormone that regulates the movement of sugar into your cells — or doesn't produce enough insulin to maintain a normal glucose level.

More common in adults, type 2 diabetes increasingly affects children as childhood obesity increases. There's no cure for type 2 diabetes, but you may be able to manage the condition by eating well, exercising and maintaining a healthy weight. If diet and exercise aren't enough to manage your blood sugar well, you also may need diabetes medications or insulin therapy.

Type 2 diabetes symptoms often develop slowly. In fact, you can have type 2 diabetes for years and not know it. Look for:

- **Increased thirst and frequent urination.** Excess sugar building up in your bloodstream causes fluid to be pulled from the tissues. This may leave you thirsty. As a result, you may drink — and urinate — more than usual.
- **Increased hunger.** Without enough insulin to move sugar into your cells, your muscles and organs become depleted of energy. This triggers intense hunger.
- **Weight loss.** Despite eating more than usual to relieve hunger, you may lose weight. Without the ability to metabolize glucose, the body uses alternative fuels stored in muscle and fat. Calories are lost as excess glucose is released in the urine.
- **Fatigue.** If your cells are deprived of sugar, you may become tired and irritable.
- **Blurred vision.** If your blood sugar is too high, fluid may be pulled from the lenses of your eyes. This may affect your ability to focus.
- **Slow-healing sores or frequent infections.** Type 2 diabetes affects your ability to heal and resist infections.
- **Areas of darkened skin.** Some people with type 2 diabetes have patches of dark, velvety skin in the folds and creases of their bodies — usually in the armpits and neck. This condition, called acanthosis nigricans, may be a sign of insulin resistance.

When to see a doctor

See your doctor if you notice any type 2 diabetes symptoms.

Type 2 diabetes develops when the body becomes resistant to insulin or when the pancreas stops producing enough insulin. Exactly why this happens is unknown, although genetics and environmental factors, such as excess weight and inactivity, seem to be contributing factors.

How insulin works

Insulin is a hormone that comes from the gland situated behind and below the stomach (pancreas).

- The pancreas secretes insulin into the bloodstream.
- The insulin circulates, enabling sugar to enter your cells.
- Insulin lowers the amount of sugar in your bloodstream.
- As your blood sugar level drops, so does the secretion of insulin from your pancreas.

The role of glucose

Glucose — a sugar — is a main source of energy for the cells that make up muscles and other tissues.

- Glucose comes from two major sources: food and your liver.
- Sugar is absorbed into the bloodstream, where it enters cells with the help of insulin.
- Your liver stores and makes glucose.
- When your glucose levels are low, such as when you haven't eaten in a while, the liver breaks down stored glycogen into glucose to keep your glucose level within a normal range.

In type 2 diabetes, this process doesn't work well. Instead of moving into your cells, sugar builds up in your bloodstream. As blood sugar levels increase, the insulin-producing beta cells in the pancreas produce more insulin, but eventually these cells become impaired and can't make enough insulin to meet the body's demands.

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In the much less common type 1 diabetes, the immune system destroys the beta cells, leaving the body with little to no insulin.

Researchers don't fully understand why some people develop type 2 diabetes and others don't. It's clear, however, that certain factors increase the risk, including:

- **Weight.** Being overweight is a primary risk factor for type 2 diabetes. The more fatty tissue you have, the more resistant your cells become to insulin. However, you don't have to be overweight to develop type 2 diabetes.
- **Fat distribution.** If your body stores fat primarily in your abdomen, your risk of type 2 diabetes is greater than if your body stores fat elsewhere, such as your hips and thighs.
- **Inactivity.** The less active you are, the greater your risk of type 2 diabetes. Physical activity helps you control your weight, uses up glucose as energy and makes your cells more sensitive to insulin.
- **Family history.** The risk of type 2 diabetes increases if your parent or sibling has type 2 diabetes.
- **Race.** Although it's unclear why, people of certain races — including blacks, Hispanics, American Indians and Asian-Americans — are more likely to develop type 2 diabetes than whites are.
- **Age.** The risk of type 2 diabetes increases as you get older, especially after age 45. That's probably because people tend to exercise less, lose muscle mass and gain weight as they age. But type 2 diabetes is also increasing dramatically among children, adolescents and younger adults.
- **Prediabetes.** Prediabetes is a condition in which your blood sugar level is higher than normal, but not high enough to be classified as diabetes. Left untreated, prediabetes can progress to type 2 diabetes.
- **Gestational diabetes.** If you developed gestational diabetes when you were pregnant, your risk of developing type 2 diabetes increases. If you gave birth to a baby weighing more than 9 pounds (4 kilograms), you're also at risk of type 2 diabetes.
- **Polycystic ovary syndrome.** For women, having polycystic ovary syndrome — a common condition characterized by irregular menstrual periods, excess hair growth and obesity — increases the risk of diabetes.

Type 2 diabetes can be easy to ignore, especially in the early stages when you're feeling fine. But diabetes affects many major organs, including your heart, blood vessels, nerves, eyes and kidneys. Controlling your blood sugar levels can help prevent these complications.

Although long-term complications of diabetes develop gradually, they can eventually be disabling or even life-threatening. Some of the potential complications of diabetes include:

- **Heart and blood vessel disease.** Diabetes dramatically increases the risk of various cardiovascular problems, including coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of arteries (atherosclerosis) and high blood pressure.
- **Nerve damage (neuropathy).** Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish your nerves, especially in the legs. This can cause tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward. Poorly controlled blood sugar can eventually cause you to lose all sense of feeling in the affected limbs. Damage to the nerves that control digestion can cause problems with nausea, vomiting, diarrhea or constipation. For men, erectile dysfunction may be an issue.
- **Kidney damage (nephropathy).** The kidneys contain millions of tiny blood vessel clusters that filter waste from your blood. Diabetes can damage this delicate filtering system. Severe damage can lead to kidney failure or irreversible end-stage kidney disease, which often eventually requires dialysis or a kidney transplant.
- **Eye damage.** Diabetes can damage the blood vessels of the retina (diabetic retinopathy), potentially leading to blindness. Diabetes also increases the risk of other serious vision conditions, such as cataracts and glaucoma.
- **Foot damage.** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can become serious infections, which may heal poorly. Severe damage might require toe, foot or leg amputation.
- **Hearing impairment.** Hearing problems are more common in people with diabetes.
- **Skin conditions.** Diabetes may leave you more susceptible to skin problems, including bacterial and fungal infections.
- **Alzheimer's disease.** Type 2 diabetes may increase the risk of Alzheimer's disease. The poorer your blood sugar control, the greater the risk appears to be. The exact connection between these two conditions still remains unclear.

Your primary care doctor will probably diagnose your type 2 diabetes. He or she may continue to treat your diabetes or may refer you to a doctor who specializes in hormonal disorders (endocrinologist). Your health care team also may include:

- Dietitian
- Certified diabetes educator
- Foot doctor (podiatrist)
- Doctor who specializes in eye care (ophthalmologist)

If your blood sugar levels are very high, your doctor may send you to the hospital for treatment.

Whenever you can, it's a good idea to prepare for appointments with your health care team. Here's some information to help you get ready for your appointment and know what to expect from your doctor.

What you can do

- **Be aware of any pre-appointment restrictions.** You may need to refrain from eating or drinking anything but water for eight hours for a fasting glucose test or four hours for a pre-meal test. When you're making an appointment, ask if you should fast.
- **Write down any symptoms you're experiencing,** including any that may seem unrelated to your diabetes.

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- **Bring a notebook and a pen or pencil** (or your laptop computer or tablet) to keep track of important information.
- **Write down questions to ask your doctor.**

Preparing a list of questions can help you make the most of your time with your doctor. For type 2 diabetes, some basic questions to ask include:

Glucose monitoring

- How often do I need to monitor my blood sugar?
- What is my goal range?
- How can I use the information from glucose monitoring to better manage my diabetes?

Lifestyle changes

- What changes do I need to make to my diet?
- How can I learn about counting carbohydrates in foods?
- Should I see a dietitian to help with meal planning?
- How much exercise should I get each day?

Medications

- Will I need to take medicine? If so, what kind and how much?
- Do I need to take the medicine at a particular time of the day?
- Do I need to take insulin?
- I have other medical problems. How can I best manage these conditions together?

Complications

- What are the signs and symptoms of low blood sugar?
- How do I treat low blood sugar?
- What are the signs and symptoms of high blood sugar?
- When should I test for ketones, and how do I do it?

Medical management

- How often do I need to be monitored for diabetes complications? What specialists do I need to see?
- Are there resources available if I'm having trouble paying for diabetes supplies?
- Are there brochures or other printed material that I can take with me? What websites do you recommend?

What to expect from your doctor

Your doctor is likely to ask you a number of questions, including:

- Do you understand your treatment plan and feel confident you can follow it?
- How are you coping with diabetes?
- Have you experienced any low blood sugar?
- What's a typical day's diet like?
- Are you exercising? If so, what type of exercise? How often?
- What challenges are you experiencing in managing your diabetes?

What you can do in the meantime

If your blood sugar is consistently out of your target range, or if you're not sure what to do in a certain situation, contact your doctor or diabetes educator.

To diagnose type 2 diabetes, you'll be given a:

- **Glycated hemoglobin (A1C) test.** This blood test indicates your average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5 percent or higher on two separate tests indicates you have diabetes. A result between 5.7 and 6.4 percent is considered prediabetes, which indicates a high risk of developing diabetes. Normal levels are below 5.7 percent.

If the A1C test isn't available, or if you have certain conditions — such as if you're pregnant or have an uncommon form of hemoglobin (known as a hemoglobin variant) — that can make the A1C test inaccurate, your doctor may use the following tests to diagnose diabetes:

- **Random blood sugar test.** A blood sample will be taken at a random time. Blood sugar values are expressed in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L). Regardless of when you last ate, a random blood sugar level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, especially when coupled with any of the signs and symptoms of diabetes, such as frequent urination and

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extreme thirst.

- **Fasting blood sugar test.** A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.
- **Oral glucose tolerance test.** For this test, you fast overnight, and the fasting blood sugar level is measured. Then you drink a sugary liquid, and blood sugar levels are tested periodically for the next two hours.

  A blood sugar level less than 140 mg/dL (7.8 mmol/L) is normal. A reading of more than 200 mg/dL (11.1 mmol/L) after two hours indicates diabetes. A reading between 140 and 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) indicates prediabetes.

The American Diabetes Association recommends routine screening for type 2 diabetes beginning at age 45, especially if you're overweight. If the results are normal, repeat the test every three years. If the results are borderline, ask your doctor when to come back for another test.

Screening is also recommended for people who are under 45 and overweight if there are other heart disease or diabetes risk factors present, such as a sedentary lifestyle, a family history of type 2 diabetes, a personal history of gestational diabetes or blood pressure above 140/90 millimeters of mercury (mm Hg).

If you're diagnosed with diabetes, the doctor may do other tests to distinguish between type 1 and type 2 diabetes — since the two conditions often require different treatments.

After the diagnosis

A1C levels need to be checked between two and four times a year. Your target A1C goal may vary depending on your age and other factors. However, for most people, the American Diabetes Association recommends an A1C level below 7 percent. Ask your doctor what your A1C target is.

Compared with repeated daily blood sugar tests, A1C testing better indicates how well your diabetes treatment plan is working. An elevated A1C level may signal the need for a change in your medication, meal plan or activity level.

In addition to the A1C test, the doctor will take blood and urine samples periodically to check your cholesterol levels, thyroid function, liver function and kidney function. The doctor will also assess your blood pressure. Regular eye and foot exams also are important.

Management of type 2 diabetes includes:

- Healthy eating
- Regular exercise
- Possibly, diabetes medication or insulin therapy
- Blood sugar monitoring

These steps will help keep your blood sugar level closer to normal, which can delay or prevent complications.

Healthy eating

Contrary to popular perception, there's no specific diabetes diet. However, it's important to center your diet on these high-fiber, low-fat foods:

- Fruits
- Vegetables
- Whole grains

You'll also need to eat fewer animal products, refined carbohydrates and sweets.

Low glycemic index foods also may be helpful. The glycemic index is a measure of how quickly a food causes a rise in your blood sugar. Foods with a high glycemic index raise your blood sugar quickly. Low glycemic foods may help you achieve a more stable blood sugar. Foods with a low glycemic index typically are foods that are higher in fiber.

A registered dietitian can help you put together a meal plan that fits your health goals, food preferences and lifestyle. He or she can also teach you how to monitor your carbohydrate intake and let you know about how many carbohydrates you need to eat with your meals and snacks to keep your blood sugar levels more stable.

Physical activity

Everyone needs regular aerobic exercise, and people who have type 2 diabetes are no exception. Get your doctor's OK before you start an exercise program. Then choose activities you enjoy, such as walking, swimming and biking. What's most important is making physical activity part of your daily routine.

Aim for at least 30 minutes of aerobic exercise most days of the week. Stretching and strength training exercises are important, too. If you haven't been active for a while, start slowly and build up gradually.

A combination of exercises — aerobic exercises, such as walking or dancing on most days, combined with resistance training, such as weightlifting or yoga twice a week — often helps control blood sugar more effectively than either type of exercise alone.

Remember that physical activity lowers blood sugar. Check your blood sugar level before any activity. You might need to eat a snack before exercising to help prevent low blood sugar if you take diabetes medications that lower your blood sugar.

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Monitoring your blood sugar

Depending on your treatment plan, you may check and record your blood sugar level every now and then or, if you're on insulin, multiple times a day. Ask your doctor how often he or she wants you to check your blood sugar. Careful monitoring is the only way to make sure that your blood sugar level remains within your target range.

Sometimes, blood sugar levels can be unpredictable. With help from your diabetes treatment team, you'll learn how your blood sugar level changes in response to food, exercise, alcohol, illness and medication.

Diabetes medications and insulin therapy

Some people who have type 2 diabetes can achieve their target blood sugar levels with diet and exercise alone, but many also need diabetes medications or insulin therapy. The decision about which medications are best depends on many factors, including your blood sugar level and any other health problems you have. Your doctor might even combine drugs from different classes to help you control your blood sugar in several different ways.

Examples of possible treatments for type 2 diabetes include:

- **Metformin (Glucophage, Glumetza, others).** Generally, metformin is the first medication prescribed for type 2 diabetes. It works by improving the sensitivity of your body tissues to insulin so that your body uses insulin more effectively.

  Metformin also lowers glucose production in the liver. Metformin usually won't lower blood sugar enough on its own. Your doctor will also recommend lifestyle changes, such as losing weight and becoming more active.

  Nausea and diarrhea are possible side effects of metformin. These side effects usually go away as your body gets used to the medicine. If metformin and lifestyles changes aren't enough to control your blood sugar level, other oral or injected medications can be added.

- **Sulfonylureas.** These medications help your body secrete more insulin. Examples of medications in this class include glyburide (DiaBeta, Glynase), glipizide (Glucotrol) and glimepiride (Amaryl). Possible side effects include low blood sugar and weight gain.
- **Meglitinides.** These medications work like sulfonylureas by encouraging the body to secrete more insulin, but they're faster acting, and they don't stay active in the body for as long. They also have a risk of causing low blood sugar, but not as much risk as sulfonylureas do.

  Weight gain is a possibility with this class of medications as well. Examples include repaglinide (Prandin) and nateglinide (Starlix).

- **Thiazolidinediones.** Like metformin, these medications make the body's tissues more sensitive to insulin. This class of medications has been linked to weight gain and other more serious side effects, such as an increased risk of heart failure and fractures. Because of these risks, these medications generally aren't a first-choice treatment.

  Rosiglitazone (Avandia) and pioglitazone (Actos) are examples of thiazolidinediones.

- **DPP-4 inhibitors.** These medications help reduce blood sugar levels, but tend to have a modest effect. They don't seem to cause weight gain. Examples of these medications are sitagliptin (Januvia), saxagliptin (Onglyza) and linagliptin (Tradjenta).
- **GLP-1 receptor agonists.** These medications slow digestion and help lower blood sugar levels, though not as much as sulfonylureas. This class of medications isn't recommended for use alone.

  Exenatide (Byetta) and liraglutide (Victoza) are examples of GLP-1 receptor agonists. Possible side effects include nausea and an increased risk of pancreatitis.

- **SGLT2 inhibitors.** These are the newest diabetes drugs on the market. They work by preventing the kidneys from reabsorbing sugar in the blood. Instead, the sugar is excreted in the urine.

  Examples include canagliflozin (Invokana) and dapagliflozin (Farxiga). Side effects may include yeast infections and urinary tract infections.

- **Insulin therapy.** Some people who have type 2 diabetes need insulin therapy as well. In the past, insulin therapy was used as last resort, but today it's often prescribed sooner because of its benefits.

  Because normal digestion interferes with insulin taken by mouth, insulin must be injected. Depending on your needs, your doctor may prescribe a mixture of insulin types to use throughout the day and night. Often, people with type 2 diabetes start insulin use with one long-acting shot at night.

  Insulin injections involve using a fine needle and syringe or an insulin pen injector — a device that looks similar to an ink pen, except the cartridge is filled with insulin.

  There are many types of insulin, and they each work in a different way. Options include:

  - Insulin glulisine (Apidra)
  - Insulin lispro (Humalog)
  - Insulin aspart (Novolog)
  - Insulin glargine (Lantus)
  - Insulin detemir (Levemir)
  - Insulin isophane (Humulin N, Novolin N)

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Discuss the pros and cons of different drugs with your doctor. Together you can decide which medication is best for you after considering many factors, including costs and other aspects of your health.

In addition to diabetes medications, your doctor might prescribe low-dose aspirin therapy as well as blood pressure and cholesterol-lowering medications to help prevent heart and blood vessel disease.

Bariatric surgery

If you have type 2 diabetes and your body mass index (BMI) is greater than 35, you may be a candidate for weight-loss surgery (bariatric surgery). Blood sugar levels return to normal in 55 to 95 percent of people with diabetes, depending on the procedure performed. Surgeries that bypass a portion of the small intestine have more of an effect on blood sugar levels than do other weight-loss surgeries.

Drawbacks to the surgery include cost, and there are risks involved, including a risk of death. Additionally, drastic lifestyle changes are required and long-term complications may include nutritional deficiencies and osteoporosis.

Pregnancy

Women with type 2 diabetes may need to alter their treatment during pregnancy. Many women use insulin therapy during pregnancy. Cholesterol-lowering medications and some blood pressure drugs can't be used during pregnancy.

If you have signs of diabetic retinopathy, it may worsen during pregnancy. Visit your ophthalmologist during the first trimester of your pregnancy and at one year postpartum.

Signs of trouble

Because so many factors can affect your blood sugar, problems sometimes arise that require immediate care, such as:

- **High blood sugar (hyperglycemia).** Your blood sugar level can rise for many reasons, including eating too much, being sick or not taking enough glucose-lowering medication. Check your blood sugar level often, and watch for signs and symptoms of high blood sugar — frequent urination, increased thirst, dry mouth, blurred vision, fatigue and nausea. If you have hyperglycemia, you'll need to adjust your meal plan, medications or both.
- **Hyperglycemic hyperosmolar nonketotic syndrome (HHNS).** Signs and symptoms of this life-threatening condition include a blood sugar reading higher than 600 mg/dL (33.3 mmol/L), dry mouth, extreme thirst, fever greater than 101 F (38 C), drowsiness, confusion, vision loss, hallucinations and dark urine. Your blood sugar monitor may not be able to give you an exact reading at such high levels and may instead just read "high."

  HHNS is caused by sky-high blood sugar that turns blood thick and syrupy. It tends to be more common in older people with type 2 diabetes, and it's often preceded by an illness or infection. HHNS usually develops over days or weeks. Call your doctor or seek immediate medical care if you have signs or symptoms of this condition.
- **Increased ketones in your urine (diabetic ketoacidosis).** If your cells are starved for energy, your body may begin to break down fat. This produces toxic acids known as ketones.

  Watch for loss of appetite, weakness, vomiting, fever, stomach pain and fruity-smelling breath. You can check your urine for excess ketones with an over-the-counter ketones test kit. If you have excess ketones in your urine, consult your doctor right away or seek emergency care. This condition is more common in people with type 1 diabetes but can sometimes occur in people with type 2 diabetes.
- **Low blood sugar (hypoglycemia).** If your blood sugar level drops below your target range, it's known as low blood sugar (hypoglycemia). Your blood sugar level can drop for many reasons, including skipping a meal or getting more physical activity than normal. Low blood sugar is most likely if you take glucose-lowering medications that promote the secretion of insulin or if you're taking insulin.

  Check your blood sugar level regularly, and watch for signs and symptoms of low blood sugar — sweating, shakiness, weakness, hunger, dizziness, headache, blurred vision, heart palpitations, slurred speech, drowsiness, confusion and seizures.

  If you develop hypoglycemia during the night, you might wake with sweat-soaked pajamas or a headache. Due to a natural rebound effect, nighttime hypoglycemia might cause an unusually high blood sugar reading first thing in the morning.

  If you have signs or symptoms of low blood sugar, drink or eat something that will quickly raise your blood sugar level — fruit juice, glucose tablets, hard candy, regular (not diet) soda or another source of sugar. Retest in 15 minutes to be sure your blood glucose levels are normal.

  If they're not, treat again and retest in another 15 minutes. If you lose consciousness, a family member or close contact may need to give you an emergency injection of a hormone that stimulates the release of sugar into the blood (glucagon).

Careful management of type 2 diabetes can reduce your risk of serious — even life-threatening — complications. Consider these tips:

- **Commit to managing your diabetes.** Learn all you can about type 2 diabetes. Make healthy eating and physical activity part of your daily routine. Establish a relationship with a diabetes educator, and ask your diabetes treatment team for help when you need it.
- **Identify yourself.** Wear a tag or bracelet that says you have diabetes.
- **Schedule a yearly physical exam and regular eye exams.** Your regular diabetes checkups aren't meant to replace regular physicals or routine eye exams. During the physical, your doctor will look for any diabetes-related complications, as well as screen for other medical problems. Your eye care specialist will check for signs of retinal damage, cataracts and glaucoma.

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- **Keep your immunizations up to date.** High blood sugar can weaken your immune system. Get a flu shot every year, and your doctor will likely recommend the pneumonia vaccine, as well. The Centers for Disease Control and Prevention (CDC) also recommends hepatitis B vaccination if you haven't previously been vaccinated against hepatitis B and you're an adult age 19 to 59 with type 1 or type 2 diabetes. The CDC advises vaccination as soon as possible after diagnosis with type 1 or type 2 diabetes. If you are age 60 or older, have diabetes and haven't previously received the vaccine, talk to your doctor about whether it's right for you.
- **Take care of your teeth.** Diabetes may leave you prone to more-serious gum infections. Brush your teeth at least twice a day, floss your teeth once a day, and schedule regular dental exams. Consult your dentist right away if your gums bleed or look red or swollen.
- **Pay attention to your feet.** Wash your feet daily in lukewarm water. Dry them gently, especially between the toes, and moisturize with lotion. Check your feet every day for blisters, cuts, sores, redness and swelling. Consult your doctor if you have a sore or other foot problem that isn't healing.
- **Keep your blood pressure and cholesterol under control.** Eating healthy foods and exercising regularly can go a long way toward controlling high blood pressure and cholesterol. Medication may be needed, too.
- **If you smoke or use other types of tobacco, ask your doctor to help you quit.** Smoking increases your risk of various diabetes complications. Talk to your doctor about ways to stop smoking or to stop using other types of tobacco.
- **If you drink alcohol, do so responsibly.** Alcohol, as well as drink mixers, can cause either high or low blood sugar, depending on how much you drink and if you eat at the same time. If you choose to drink, do so in moderation and always with a meal.

  The recommendation is no more than one drink daily for women, no more than two drinks daily for men age 65 and younger, and one drink a day for men over 65. If you're on insulin or other medications that lower your blood sugar, check your blood sugar before you go to sleep to make sure you're at a safe level.

Numerous alternative medicine substances have been shown to improve insulin sensitivity in some studies, while other studies fail to find any benefit for blood sugar control or in lowering A1C levels. Because of the conflicting findings, no alternative therapies are recommended to help with blood sugar management.

If you decide to try an alternative therapy, don't stop taking the medications that your doctor has prescribed. Be sure to discuss the use of any of these therapies with your doctor to make sure that they won't cause adverse reactions or interact with your medications.

No treatments — alternative or conventional — can cure diabetes. So it's critical that people who are using insulin therapy for diabetes don't stop using insulin unless directed to do so by their physicians.

Type 2 diabetes is a serious disease, and following your diabetes treatment plan takes round-the-clock commitment. But your efforts are worthwhile because following your treatment plan can reduce your risk of complications.

Talking to a counselor or therapist may help you cope with the lifestyle changes that come with a type 2 diabetes diagnosis. You may find encouragement and understanding in a type 2 diabetes support group. Although support groups aren't for everyone, they can be good sources of information. Group members often know about the latest treatments and tend to share their own experiences or helpful information, such as where to find carbohydrate counts for your favorite takeout restaurant. If you're interested, your doctor may be able to recommend a group in your area.

Or, you can visit the American Diabetes Association to check out local activities and support groups for people with type 2 diabetes. The American Diabetes Association also offers online information and online forums where you can chat with others who have diabetes. The phone number is 800-DIABETES (800-342-2383).

Healthy lifestyle choices can help you prevent type 2 diabetes. Even if you have diabetes in your family, diet and exercise can help you prevent the disease. If you've already received a diagnosis of diabetes, you can use healthy lifestyle choices to help prevent complications. And if you have prediabetes, lifestyle changes can slow or halt the progression from prediabetes to diabetes.

- **Eat healthy foods.** Choose foods lower in fat and calories and higher in fiber. Focus on fruits, vegetables and whole grains.
- **Get physical.** Aim for 30 minutes of moderate physical activity a day. Take a brisk daily walk. Ride a bike. Swim laps. If you can't fit in a long workout, spread 10-minute or longer sessions throughout the day.
- **Lose excess pounds.** If you're overweight, losing 7 percent of your body weight can reduce the risk of diabetes. To keep your weight in a healthy range, focus on permanent changes to your eating and exercise habits. Motivate yourself by remembering the benefits of losing weight, such as a healthier heart, more energy and improved self-esteem.

Sometimes medication is an option as well. Metformin (Glucophage, Glumetza, others), an oral diabetes medication, may reduce the risk of type 2 diabetes — but healthy lifestyle choices remain essential.

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Type 2 diabetes - information prescription

Treating type 2 diabetes

Medicines for type 2 diabetes

Type 2 diabetes usually gets worse over time. Making lifestyle changes, such as adjusting your diet and taking more exercise, may help you control your blood glucose levels at first, but they not be enough in the long term.

You may eventually need to take medication to help control your blood glucose levels. Initially, this will usually be in the form of tablets, and can sometimes be a combination of more than one type of tablet. It may also include insulin or other medication that you inject.

Metformin

Metformin is usually the first medicine that's used to treat type 2 diabetes. It works by reducing the amount of glucose that your liver releases into your bloodstream. It also makes your body's cells more responsive to insulin.

Metformin is recommended for adults with a high risk of developing type 2 diabetes, whose blood glucose is still progressing towards type 2 diabetes, despite making necessary lifestyle changes.

If you're overweight, it's also likely you'll be prescribed metformin. Unlike some other medicines used to treat type 2 diabetes, metformin shouldn't cause additional weight gain.

However, it can sometimes cause mild side effects, such as nausea and diarrhoea, and you may not be able to take it if you have kidney damage.

Sulphonylureas

Sulphonylureas increase the amount of insulin that's produced by your pancreas. Examples of sulphonylureas include:

- glibenclamide
- gliclazide
- glimepiride
- glipizide
- gliquidone

You may be prescribed one of these medicines if you can't take metformin, or if you aren't overweight. Alternatively, you may be prescribed sulphonylurea and metformin if metformin doesn't control blood glucose on its own.

Sulphonylureas can increase the risk of hypoglycaemia (low blood sugar), because they increase the amount of insulin in your body. They can also sometimes cause side effects including weight gain, nausea and diarrhoea.

Glitazones (thiazolidinediones, TZDs)

Thiazolidinedione medicines (pioglitazone) make your body's cells more sensitive to insulin so that more glucose is taken from your blood.

They're usually used in combination with metformin or sulphonylureas, or both. They may cause weight gain and ankle swelling (oedema). You shouldn't take pioglitazone if you have heart failure or a high risk of bone fracture.

Another thiazolidinedione, rosiglitazone, was withdrawn from use in 2010 due to an increased risk of cardiovascular disorders, including heart attack and heart failure.

Read more about the withdrawal of rosiglitazone.

Gliptins (DPP-4 inhibitors)

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Gliptins work by preventing the breakdown of a naturally occurring hormone called GLP-1. GLP-1 helps the body produce insulin in response to high blood glucose levels, but is rapidly broken down.

By preventing this breakdown, the gliptins (linagliptin, saxagliptin, sitagliptin and vildagliptin) prevent high blood glucose levels, but don't result in episodes of hypoglycaemia.

You may be prescribed a gliptin if you're unable to take sulphonylureas or glitazones, or in combination with them. They're not associated with weight gain.

GLP-1 agonists

Exenatide is a GLP-1 agonist, an injectable treatment that acts in a similar way to the natural hormone GLP-1 (see the section on gliptins, above).

It's injected twice a day and boosts insulin production when there are high blood glucose levels, reducing blood glucose without the risk of hypoglycaemia episodes ("hypos").

It also leads to modest weight loss in many people who take it. It's mainly used in people on metformin plus sulphonylurea, who are obese. A once-weekly product has also been introduced.

Another GLP-1 agonist called liraglutide is a once-daily injection (exenatide is given twice a day). Like exenatide, liraglutide is mainly used for people on metformin plus sulphonylurea, who are obese, and in clinical trials it's been shown to cause modest weight loss.

Acarbose

Acarbose helps prevent your blood glucose level from increasing too much after you eat a meal. It slows down the rate at which your digestive system breaks carbohydrates down into glucose.

Acarbose isn't often used to treat type 2 diabetes because it usually causes side effects, such as bloating and diarrhoea. However, it may be prescribed if you can't take other types of medicine for type 2 diabetes.

Nateglinide and repaglinide

Nateglinide and repaglinide stimulate the release of insulin by your pancreas. They're not commonly used, but may be an option if you have meals at irregular times. This is because their effects don't last very long, but they're effective when taken just before you eat.

Nateglinide and repaglinide can cause side effects, such as weight gain and hypoglycaemia (low blood sugar).

Insulin treatment

If glucose-lowering tablets aren't effective in controlling your blood glucose levels, you may need to have insulin treatment. This can be taken instead of or alongside your tablets, depending on the dose and the way that you take it.

Insulin comes in several different preparations, and each works slightly differently. For example, some last up to a whole day (long-acting), some last up to eight hours (short-acting) and some work quickly but don't last very long (rapid-acting).

Your treatment may include a combination of these different insulin preparations.

Insulin injections

Insulin must be injected because if it were taken as a tablet, it would be broken down in your stomach like food and unable to enter your bloodstream.

If you need to inject insulin, your diabetes care team will advise you about when you need to do it. They will show you how to inject it yourself and will also give you advice about storing your insulin and disposing of your needles properly.

Insulin injections are given using either a syringe or an injection pen, which is also called an insulin pen (auto-injector). Most people need between two and four injections of insulin a day.

Your GP or diabetes nurse will also teach a relative or a close friend how to inject the insulin properly.

You can read more about insulin and how to inject it on the Diabetes UK website.

Treatment for low blood sugar (hypoglycaemia)

If you have type 2 diabetes that's controlled using insulin or certain types of tablets, you may experience episodes of hypoglycaemia.

Hypoglycaemia is where your blood glucose levels become very low. Mild hypoglycaemia (a "hypo") can make you feel shaky, weak and hungry, but it can usually be controlled by eating or drinking something sugary.

If you have a hypo, you should initially have a form of carbohydrate that will act quickly, such as a sugary drink or glucose tablets. This should be followed by a longer-acting carbohydrate, such as a cereal bar, sandwich or piece of fruit. In most cases, these measures will be enough to raise your blood glucose level to normal, although it may take a few hours.

If you develop severe hypoglycaemia, you may become drowsy and confused, and you may even lose consciousness. If this occurs, you may need to have an injection of glucagon into your muscle or glucose into a vein. Glucagon is a hormone that quickly increases your blood glucose levels.

Your diabetes care team can advise you on how to avoid a hypo and what to do if you have one.

Other treatments

If you have type 2 diabetes, your risk of developing heart disease, stroke and kidney disease is increased.

To reduce your risk of developing other serious health conditions, you may be advised to take other medicines, including:

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- anti-hypertensive medicines to control high blood pressure

- a statin, such as simvastatin or atorvastatin, to reduce high cholesterol
- low-dose aspirin to prevent a stroke
- an angiotensin-converting enzyme (ACE) inhibitor, such as enalapril, lisinopril or ramipril, if you have the early signs of diabetic kidney disease

Diabetic kidney disease is identified by the presence of small amounts of albumin (a protein) in your urine. If treated early enough, it may be reversible.

Monitoring blood glucose levels

If you have type 2 diabetes, your GP or diabetes care team will need to take a reading of your blood glucose level about every two to six months. This will show how stable your glucose levels have been in the recent past and how well your treatment plan is working.

The HbA1c test is used to measure blood glucose levels over the previous two to three months. HbA1c is a form of haemoglobin, the chemical that carries oxygen in red blood cells, which also has glucose attached to it.

A high HbA1c level means that your blood glucose level has been consistently high over recent weeks, and your diabetes treatment plan may need to be changed.

Your diabetes care team can help you set a target HbA1c level to aim for. This will usually be less than 59mmol/mol (7.5%). However, it can be as low as 48mmol/mol (6.5%) for some people.

Read more about the HbA1c test.

Monitoring your own blood glucose

If you have type 2 diabetes, as well as having your blood glucose level checked by a healthcare professional every two to six months, you may be advised to monitor your own blood glucose levels at home.

Even if you have a healthy diet and are taking tablets or using insulin therapy, exercise, illness and stress can affect your blood glucose levels. Other factors that may affect your blood glucose levels include drinking alcohol, taking other medicines and, for women, hormonal changes during the menstrual cycle.

A blood glucose meter is a small device that measures the concentration of glucose in your blood. It can be useful in detecting high blood sugar (hyperglycaemia) or low blood sugar (hypoglycaemia).

If blood glucose monitoring is recommended, you should be trained in how to use a blood glucose meter and what you should do if the reading is too high or too low.

Blood glucose meters aren't currently available for free on the NHS but, in some cases, blood monitoring strips may be. Ask a member of your diabetes care team if you're unsure.

Diabetes UK also provides further information about the availability of blood glucose test strips (PDF, 195kb).

Regularly monitoring your blood glucose levels will ensure that your blood glucose is as normal and stable as possible. As your blood glucose level is likely to vary throughout the day, you may need to check it several times a day, depending on the treatment you're taking.

In home testing, blood glucose levels are usually measured by how many millimoles of glucose are in a litre of blood. A millimole is a measurement used to define the concentration of glucose in your blood. The measurement is expressed as millimoles per litre, or mmol/l for short.

A normal blood glucose level is 4-6 mmol/l before meals (preprandial) and less than 10 mmol/l two hours after meals (postprandial), although this can vary from person to person. Your diabetes care team can discuss your blood glucose level with you in more detail.

Care standards for diabetes

The aim of treating diabetes is to help people with the condition control their blood glucose levels and minimise the risk of developing future complications.

The Department of Health has set out national standards for NHS organisations and professionals covering diabetes care and prevention. The diabetes national service framework was developed by diabetes clinical experts and diabetes patients. Good diabetes care includes:

- awareness of the risk factors for type 2 diabetes
- advice and support to help people at risk of type 2 diabetes reduce that risk
- access to information and appropriate support for people with type 1 diabetes and type 2 diabetes, including access to a structured education programme, such as the Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) or X-PERT Health
- an agreed care plan to help all people with diabetes to manage their care and lead a healthy lifestyle, including a named contact for their care
- information, care and support to enable all people with diabetes to optimise their blood glucose level, maintain an acceptable blood pressure and minimise other risk factors for developing complications
- access to services to identify and treat possible complications, such as screening for diabetic retinopathy and specialised foot care
- effective care for all people with diabetes admitted to hospital, for whatever reason

You can read more about diabetes care on the Diabetes UK website.

Additional information

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Useful organisations

Diabetes UK

Macleod House, 10 Parkway, London, NW1 7AA
Tel : 0845 120 2960

http://www.diabetes.org.uk/

NHS Choices puts you in control of your healthcare

The NHS Choices has been developed to help you make choices about your health, from lifestyle decisions about things like smoking, drinking and exercise, through to the practical aspects of finding and using NHS services when you need them.

www.nhs.uk

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American Diabetes Association.
75TH ANNIVERSARY ESTABLISHED 1940

American Diabetes Association
1701 North Beauregard Street
Alexandria, VA 22311
1-800-DIABETES (800-342-2383)

What Are My Options?

There are different types, or classes, of drugs that work in different ways to lower blood glucose (blood sugar) levels:

- Sulfonylureas
- Biguanides
- Meglitinides
- Thiazolidinediones
- DPP-4 inhibitors
- SGLT2 Inhibitors
- Alpha-glucosidase inhibitors
- Bile Acid Sequestrants

Sulfonylureas

Sulfonylureas stimulate the beta cells of the pancreas to release more insulin. Sulfonylurea drugs have been in use since the 1950s. Chlorpropamide (Diabinese) is the only first-generation sulfonylurea still in use today. The second generation sulfonylureas are used in smaller doses than the first-generation drugs. There are three second-generation drugs: glipizide (Glucotrol and Glucotrol XL), glyburide (Micronase, Glynase, and Diabeta), and glimepiride (Amaryl). These drugs are generally taken one to two times a day, before meals. All sulfonylurea drugs have similar effects on blood glucose levels, but they differ in side effects, how often they are taken, and interactions with other drugs.

Biguanides

Metformin (Glucophage) is a biguanide. Biguanides lower blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin so glucose can be absorbed. It is usually taken two times a day. A side effect of metformin may be diarrhea, but this is improved when the drug is taken with food.

Meglitinides

Meglitinides are drugs that also stimulate the beta cells to release insulin. Repaglinide (Prandin) and nateglinide (Starlix) are meglitinides. They are taken before each of three meals.

Because sulfonylureas and meglitinides stimulate the release of insulin, it is possible to

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have hypoglycemia (low blood glucose levels).

You should know that alcohol and some diabetes pills may not mix. Occasionally, chlorpropamide and other sulfonylureas, can interact with alcohol to cause vomiting, flushing or sickness. Ask your doctor if you are concerned about any of these side effects.

Thiazolidinediones

Rosiglitazone (Avandia) and pioglitazone (ACTOS) are in a group of drugs called thiazolidinediones. These drugs help insulin work better in the muscle and fat and also reduce glucose production in the liver. The first drug in this group, troglitazone (Rezulin), was removed from the market because it caused serious liver problems in a small number of people. So far rosiglitazone and pioglitazone have not shown the same problems, but users are still monitored closely for liver problems as a precaution. Both drugs appear to increase the risk for heart failure in some individuals, and there is debate about whether rosiglitazone may contribute to an increased risk for heart attacks. Both drugs are effective at reducing A1C and generally have few side effects.

DPP-4 Inhibitors

A new class of medications called DPP-4 inhibitors help improve A1C without causing hypoglycemia. They work by by preventing the breakdown of a naturally occurring compound in the body, GLP-1. GLP-1 reduces blood glucose levels in the body, but is broken down very quickly so it does not work well when injected as a drug itself. By interfering in the process that breaks down GLP-1, DPP-4 inhibitors allow it to remain active in the body longer, lowering blood glucose levels only when they are elevated. DPP-4 inhibitors do not tend to cause weight gain and tend to have a neutral or positive effect on cholesterol levels. Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina) are the DPP-4 inhibitors currently on the market in the US.

SGLT2 Inhibitors

Glucose in the bloodstream passes through the kidneys, where it can either be excreted or reabsorbed. Sodium-glucose transporter 2 (SGLT2) works in the kidney to reabsorb glucose, and a new class of medication, SGLT2 inhibitors, block this action, causing excess glucose to be eliminated in the urine. Canagliflozin (Invokana) and dapagliflozin (Farxiga) are SGLT2 inhibitors that have recently been approved by the FDA to treat type 2 diabetes. Because they increase glucose levels in the urine, side effects can include urinary tract and yeast infections.

Alpha-glucosidase inhibitors

Acarbose (Precose) and miglitol (Glyset) are alpha-glucosidase inhibitors. These drugs help the body to lower blood glucose levels by blocking the breakdown of starches, such

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as bread, potatoes, and pasta in the intestine. They also slow the breakdown of some sugars, such as table sugar. Their action slows the rise in blood glucose levels after a meal. They should be taken with the first bite of a meal. These drugs may have side effects, including gas and diarrhea.

Bile Acid Sequestrants

The bile acid sequestrant (BAS) colesevelam (Welchol) is a cholesterol-lowering medication that also reduces blood glucose levels in patients with diabetes. BASs help remove cholesterol from the body, particularly LDL cholesterol, which is often elevated in people with diabetes. The medications reduce LDL cholesterol by binding with bile acids in the digestive system; the body in turn uses cholesterol to replace the bile acids, which lowers cholesterol levels. The mechanism by which colesevelam lowers glucose levels is not well understood. Because BASs are not absorbed into the bloodstream, they are usually safe for use by patients who may not be able to use other medications because of liver problems. Because of the way they work, side effects of BASs can include flatulence and constipation.

Oral combination therapy

Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. For example, a biguanide and a sulfonylurea may be used together. Many combinations can be used. Though taking more than one drug can be more costly and can increase the risk of side effects, combining oral medications can improve blood glucose control when taking only a single pill does not have the desired effects. Switching from one single pill to another is not as effective as adding another type of diabetes medicine.

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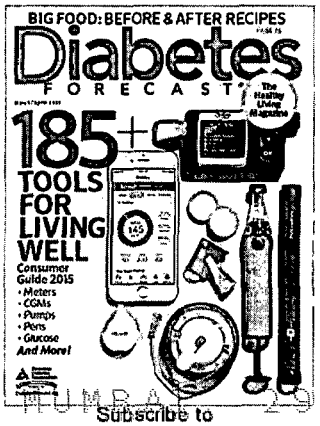

Articles from *Diabetes Forecast® magazine: (http://www.diabetesforecast.org)*

(http://www.diabetes.org/in-my-community/become-a-member/?loc=articles)
How Do Diabetes Medications Work?
(http://www.diabetesforecast.org/2015/mar-apr/how-do-diabetes-

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New Combo Drugs Control Diabetes
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(http://www.diabetesforecast.org/2014/05-may/should-i-take-metformin-with.html?loc=morefrom)

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ANNEXURE-J

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Journal of Diabetology, October 2013; 3:4 **http://www.journalofdiabetology.org/**

Original Article:

Economic burden of diabetes in people living with the disease; a field study

*A.C.V. Loganathan, K.R. John

Abstract

Diabetes Mellitus is a growing epidemic and the cost of treating diabetes is largely increasing. The objective of the study was to assess and quantify the economic burden of treating diabetes in Chennai among various socio-economic groups with a specific focus on middle-income and middle-aged group. A prevalence-based 'Cost-of-Illness' study for diabetes care was conducted in six different outpatient clinics located in Chennai, India during the months of May and August 2011. A pre-tested questionnaire was administered to collect the data from 100 randomly selected persons with diabetes. The annual mean direct cost for each person with diabetes was estimated to be Indian Rupee (INR) 23,818 (USD 380). The INR 22, 720 (USD 363) spent on medicines accounted for the largest share of direct costs (95%). Comparing annual median direct medical cost incurred by different income groups of people with diabetes, the study revealed that the middle-income group incurs 74% less direct medical costs than the lower income group and no significant difference with high-income groups. The middle-aged group incurs 80% more direct medical costs than their younger counterparts, but 17% more compared to the higher age group. The study found that age, gender and education levels had no significant role in affecting the medical costs. This study concluded that people with diabetes make substantial expenditures – costs that can be saved by prevention, public awareness and health insurance plans specific to diabetes care. Research and programmes need to be initiated to minimize costs and prevent the epidemic.

Key words: Diabetes Mellitus, economic burden, substantial expenditures, cost

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Introduction

Diabetes mellitus, also known as diabetes, is a metabolic disease in which a person has high blood glucose, either because the body does not produce enough insulin, or their cells do not respond to the insulin produced. People with diabetes develop further health complications as a result of inadequate blood sugar control, a condition that can lead to heart disease and stroke, as well as damage to kidneys, nerves and retina.

Diabetes is a major health problem worldwide, which affects a significant percentage of the Indian population. According to the International Diabetes Federation, in 2012, more than 371 million people worldwide have diabetes (1). In India, 63 million people have diabetes as of 2012, and the number is estimated to increase to 101 million by 2030 (2).

The diabetes epidemic is more pronounced in urban areas in India, where rates of diabetes are roughly double than the rural areas. Diabetes consumes between 5% and 25% of the income of an average Indian family, which translates to USD 2.2 billion a year on diabetes care and treatment (3). Many patients are unaware of treatment expenses and are not able to plan the budget. In developed countries, diabetes alone claims on average around 8% of total health care budgets (4). The per capita expenditure on health care in India is only 6.4% of average world spending (5). The direct healthcare cost of diabetes is estimated

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to be at least USD 153 billion annually for people in the 20 to 79 age group (6).

The rationale behind undertaking this study is primarily two-fold; various studies indicate that there is a high financial impact on society from the cost of diabetes care and treatment; although there are one or two studies focused on Chennai city on the cost of diabetes, the researchers recognized the need for a new study. For instance, a previous study (7) focused on comparing urban versus rural populations over a period of seven years and what was defined as 'higher family annual income Indian Rupee (INR) 100,000 in urban subjects is no longer considered higher income. The present study found that amount to be a low income among the people surveyed in the study. A fresh insight is needed into the economic burden of diabetes as Chennai city has been continually growing and family incomes have been rising steadily.

The importance of studying the economic burden of diabetes in India assumes significance, as the knowledge of the costs of diabetes improves our understanding of the importance of addressing healthcare issues and preventive methods associated with diabetes. Presenting the data helps to create public awareness and can help policy makers plan to curb the disease and increase the provision of treatment facilities, as well as prioritizing healthcare and research. The study analyzed the cost impact of other diseases caused by diabetes, such as heart disease and stroke.

Methodology

The study was carried out in 6 outpatient diabetic clinics of Chennai during 2 months, May and August 2011. A pre-tested survey questionnaire was used to collect the data from 100 randomly selected people with diabetes. The survey questionnaire consisted of 4 sections and 30 questions to gather data on demographics, diagnosis and treatment expenditures. About 50% of the questions focused on direct medical, direct non-medical and indirect costs of diabetes care.

The study was approved by the medical college research and ethics committee prior to starting the research. The questionnaire was administered individually to all people with diabetes (patient consent was obtained prior to conducting the survey).

The collected data were verified for consistency and accuracy with the clinic doctors treating the person with diabetes and the typical price of the medicine from pharmacy stores in the area was recorded. Data were analyzed on the Statistical Package for the Social Sciences (SPSS) software version 16, and MS-Excel spread sheet. The study result obtained through analysis helped quantify economic burden of diabetes care with split of direct medical and non-medical costs.

This study population of 100 is due to small catchment of the survey of 6 outpatient diabetes clinics in Chennai conducted over just 2 months, May and August, 2011.

Direct costs constitute a sizeable share of the total cost of diabetes. Direct costs include: accommodation, transportation, medication, consultation.

Indirect costs do not make as great an impact as direct costs. However, they are just as important. Indirect costs include increased absenteeism, reduced productivity and unemployment due to disease-related disability.

Study Questionnaire Design

The questions addressed to the patients were from four sections, Demography (8 questions), Lifestyle and Diabetes focused (8), Direct Medical Cost related (8), and Direct Non-Medical Cost related (9).

The questionnaire included

1. Personal data such as age, gender, occupation and socio-economic class
2. How long the subject has been diagnosed with diabetes
3. Direct medical cost per annum
   a. Annual cost spent on consultation
   b. Annual cost spent on medicines
   c. In the last 6 months, how much you spent on hospital fees

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4. Direct nonmedical cost per annum
   a. Annual cost spent on transportation
   b. Annual household expenses (maid-servant/child care)
5. Indirect cost per annum
   a. Approximately how much have you spent on your special diet
6. Any other disease the patient has as a result of diabetes. How much is spent on the treatment of the other disease vs. diabetes.

Study Execution

Although the questionnaire was designed in English, the participants were asked in Tamil, the local language.

Data analysis

The data collected were analysed using Statistical Package for Social Sciences (SPSS) software version 16 and Ms-Excel spread sheet. Mean and standard deviations were calculated for all the variables related to cost.

Results

The study was based on 100 people with diabetes at six outpatient diabetic clinics across Chennai, India. The survey participants with diabetes were identified to meet the study criteria of 'middle age' (48%) and 'middle income' (69%). The data were collected by interviewing the people using a questionnaire developed for the study. A sample questionnaire was first piloted on 20 people and then later revised with few necessary adjustments based on the applicability and response to questions.

Key observations of the participants from a demographic perspective were: the average age was 57.23 (for males it was 58.83 and for females 55.81). The age of most of the people varied between the 42 and 56. There was a spike in the data in 45-55 and 70-75 age ranges as seen in Graph 1: 'Age Distribution'. This confirms that people in middle age (45-55) are at increased risk for type-2 diabetes. Most of the people with diabetes had been diagnosed only 2 years before but overall the disease duration varied from 1 month to 30 years as seen in Graph 2: 'Length of Diabetes'

Only 13% of the participants were taking insulin, while 87% were on oral medication. This is line with the fact that the majority of the people have type 2 diabetes, as seen in graph 3. On an average, people visited their diabetes clinic every 3 months.

The cost components of providing treatment and care for people with diabetes classified into direct medical and non-medical cost. The largest proportion of the total cost was made up of direct medical costs (92%) and direct non-medical costs (8%). The mean annual direct medical cost is INR 23,818.16 (USD 380); that of direct non-medical cost is INR 7,310.30 (USD 117). The study found that the middle-income participants incur 74% less average yearly direct medical costs than the lower-income groups and there was no significant difference with high-income groups. The middle-age group incurs 80% more average yearly direct medical costs than their younger counterparts and 17% more compared with the higher-age group.

Discussion

Diabetes is a chronic and costly disease and has a significant economic impact on people with diabetes, families, healthcare institutions and productivity. A lot of variables will determine the costs of a particular illness. These include: the type of disease; the number and severity of disease complications; the demographic profile of the patient population (8). The level of education and the socioeconomic status of the person with diabetes both play a role in the cost of diabetes care.

The total cost of treating diabetes was on average INR 31,198.98 (USD 498) per person per year. The study also identified the components of the cost of care. The total cost break-down is INR 23,818.16 (USD 380) (76.3%) for direct medical-related and INR 7380.82 (USD 118) (23.7%) indirect medical-related expenses [Table 2]. A significant portion of the expenses came from prescription expenditures: 24% of the direct medical costs.

Regarding the socioeconomic and demographic characteristics of the study, there were significant findings [Table 3] as described here.

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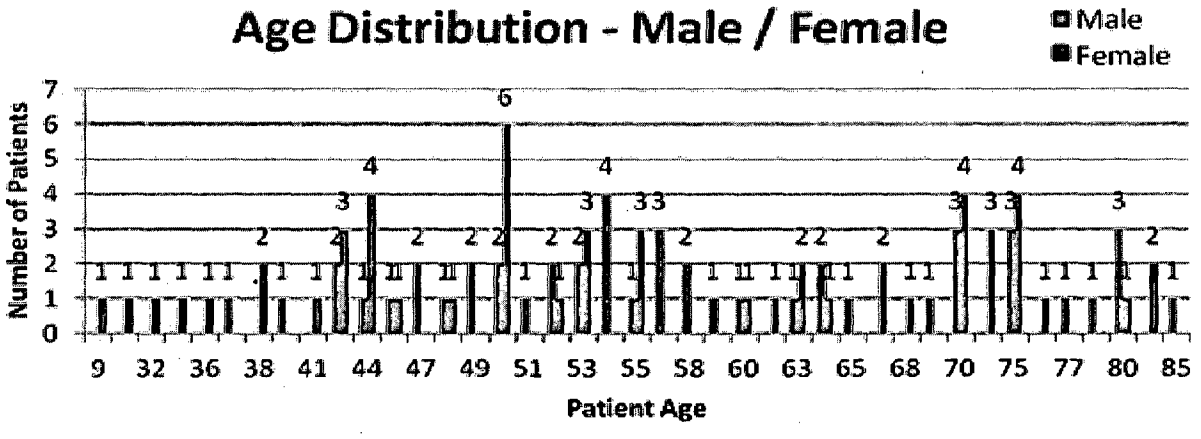
Table 1: Demographic profile of people with diabetes

		Gender		
		Total subjects (%)	Male	Female
Age range	< 45	19	5	14
	45 - 64	48	28	20
	> 65	32	14	18
Education level	Nil	14	3	11
	Non-High school	15	8	7
	High school	42	20	22
	Diploma	3	3	0
	Degree	23	13	10
Income level	< 1 lakh	25	7	18
	1 – 6 lakh	69	37	32
	> 6 lakh	5	3	2
Occupation	Unemployed	41	3	38
	Private	19	12	7
	Government	12	9	3
	Business	8	7	1
	Retired	19	16	3



Graph 1: Age Distribution – Male vs. Female

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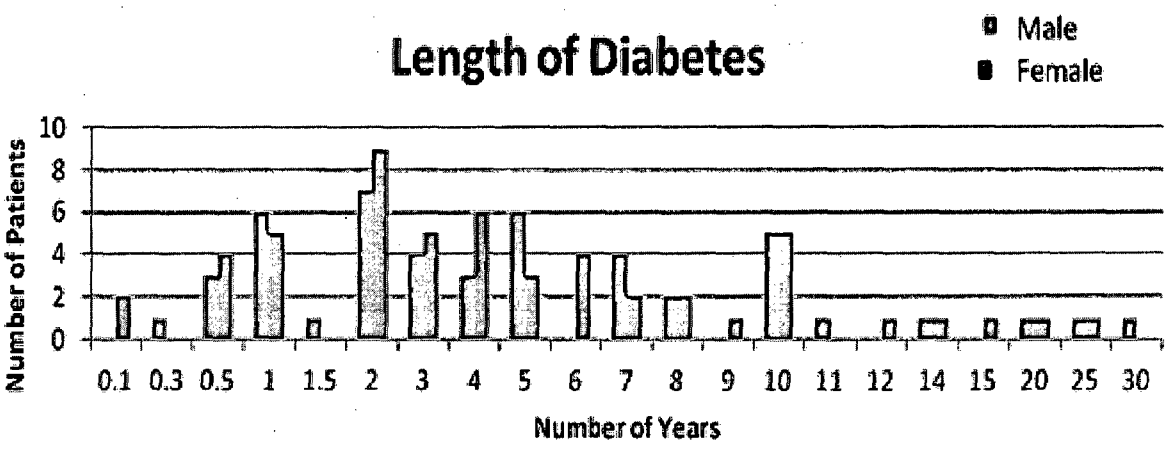
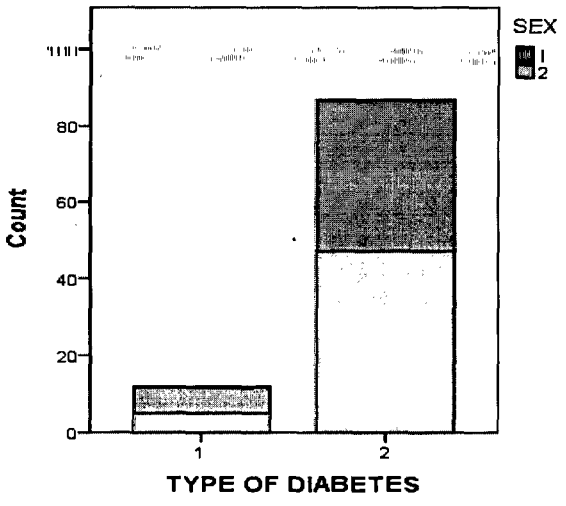


Graph 2: Duration of Diabetes – Male vs. Female



Graph 3: Number of males and females vs. type of diabetes (1 – Male; 2 – Female)

Education and income level have a clear bearing on the cost of diabetes care and the consequent economic burden. The median and mean direct medical cost of higher-income subjects (68% in 2 to 5 lakh INR) is lower by 23% than the low-income groups (25% in 1 lakh annual income). This may be attributed to levels of disease awareness and the affordability of early diagnosis.

The annual income of those surveyed is the total annual earnings of the household – determined based on the net income of each member of the household. The survey findings indicated an annual income range of 1 to 5 lakhs INR for the study population. For the purpose of analysis, the study population was categorized into two groups, lower and higher income, the latter representing household earning of 2 to 5 lakhs INR. The study indicated a marked difference in the cost of diabetes treatment between the two income groups, a key factor in determining the economic burden of the disease. The study reveals that the cost of treatment and household income has an impact on each other. The household income difference has the potential to play an important role in the economic burden of the disease, regardless of actual income, which can be validated by extending the present study over a larger population and income range.

Interestingly, the age range has less impact on the cost of care. This can be seen in the finding that the median and mean direct medical costs do not differ greatly for the age groups, 45-64 (47%) and above 65 years (32%). Similarly, no significant difference was found in the direct medical cost between male and female participants.

There is a close relationship between type of diabetes and type of medication: type I diabetes is typically insulin dependent and the direct medical cost shows this relationship. There is a clear impact by the duration of the disease factor as the mean expense of the group (below 6 years, 64%) is 37% lower than that of the group, which has the disease for 6 to 10 years (25%).

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Table 2: Direct and Indirect Medical Cost

	Amount spent per test	Annual cost of consultation	Annual cost of medication	Annual cost of transportation	Amount spent on emergency visits	Direct medical cost	Indirect medical cost
N	99	99	98	99	99	98	99
Mean	338.69	763.64	22720.41	1724.44	5585.86	23818.16	7310.30
Median	250.00	400.00	6000.00	240.00	0.00	6550.00	250.00
Std. Error of Mean	21.97	196.64	3921.55	334.09	5056.66	3942.79	5111.90
Minimum	30.00	100.00	1200.00	0.00	0.00	1430.00	0.00
Maximum	750.00	18000.00	132000.00	24000.00	500000.00	133650.00	506000.00
Std. Deviation	218.63	1956.57	38821.37	3324.12	50313.10	39031.64	50862.73

Although the results of this study cannot be matched with other studies mainly because of social and economic differences, a measure of perspective can be derived by looking at the findings from other studies. For instance, a 2009 study involving people with diabetes in the coastal district of Karnataka found annual medicine costs of INR 16,324.7 (USD 261) as compared with INR 23,818.00 (USD 380) from this study (9). The difference might be attributable to the increase in medicine costs over the past 2 years, and the fact that Chennai is a major metropolitan city, and coastal Karnataka is a semi-urban area.

A similar comparison between this study and a study conducted in 2000 in Chennai indicated that the annual median direct cost has doubled from INR 4510 (USD 72) (10) as compared to INR 6550 (USD 105) in our study, reflecting the increase in costs over the decade. A 2005 study (11) on the cost of diabetes care in north India revealed that annual cost of care was INR 14,508 (68% of total cost), and by comparison our study found the median annual direct cost as INR 23,818 (76%). The findings of our study correlate with previous studies conducted in Chennai and two other parts of India.

There are some limitations in the study that can be improved on to provide a more accurate result. These limitations include the sample size (due to study population and time), socioeconomic groups (due to study location) and the size of the clinics/hospitals (the medical costs will vary).

The experimental design and survey questionnaire helped gather the required data for the study. The constituents of the questionnaire aided in correctly assessing the different socio-economic groups and the factors affecting the economic burden of treating diabetes. The statistical analysis tools, SPSS package and MS-Excel enabled us to analyse successfully the raw data gathered and gain insight in order to test hypotheses on the cost of diabetes care and the corresponding economic burden on different socio-economic groups and how these affect the demographics of the people with diabetes. Analysis of the study data enabled the identification of the key components affecting the economic burden of diabetes treatment. As hypothesized, the cost of medicine was the biggest factor in the cost of diabetes treatment.

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Table 3: Statistical Analysis of Cost of Diabetes Care by Income Level

Income level 1) < 1 lakh 2) 1 to < 6 3) > 6 lakh		Annual cost of consultation	Amount spent per test	Annual cost of medication	Cost of emergency visits	Annual cost of transportation	Total cost
1	N	25	25	25	25	25	25
	Mean	468.00	355.20	34104.00	520.00	2972.00	4474.4000
	Median	400.00	250.00	6000.00	.00	2000.00	1360.0000
	Std. Error of Mean	64.928	51.572	9441.611	412.795	693.267	996.36859
	Minimum	100	50	1200	0	0	510.00
	Maximum	1200	750	132000	10000	12000	16850.00
	Std. Deviation	324.641	257.862	47208.054	2063.977	3466.333	4981.84293
	% of Total N	25.3%	25.3%	25.5%	25.3%	25.3%	25.5%
2	N	69	69	68	69	69	68
	Mean	855.07	342.75	18864.71	7826.09	1247.83	10355.7353
	Median	400.00	250.00	6000.00	.00	200.00	1100.0000
	Std. Error of Mean	279.456	25.093	4340.107	7253.066	390.802	7386.97319
	Minimum	100	30	1200	0	0	450.00
	Maximum	18000	750	132000	500000	24000	503530.00
	Std. Deviation	2321.339	208.439	35789.441	60248.494	3246.247	60914.541
	% of Total N	69.7%	69.7%	69.4%	69.7%	69.7%	69.4%
3	N	5	5	5	5	5	5
	Mean	980.00	200.00	18240.00	.00	2064.00	2264.0000
	Median	800.00	250.00	3000.00	.00	2000.00	1200.0000
	Std. Error of Mean	400.500	38.730	11251.560	.000	1066.628	1006.15406
	Minimum	100	50	1200	0	120	520.00
	Maximum	2400	250	60000	0	6000	5950.00
	Std. Deviation	895.545	86.603	25159.253	.000	2385.053	2249.82888
	% of Total N	5.1%	5.1%	5.1%	5.1%	5.1%	5.1%

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Conclusion

The population of Chennai city has been increasing steadily and the rapid rise of its middle-class population is going through a significant change in lifestyle and dietary habits, two key factors behind type 2 diabetes. The currently available data indicate that over the period 1989 to 2004, diabetes prevalence in Chennai increased by 72% to 14.3%. About 10.6% of the population of the state of Tamil Nadu has some form of insulin imbalance and Chennai, the capital city, constitutes 6.49% of the total state population. The state's 41 lakh people with diabetes include 13.8% from towns and cities and 8% from rural areas. Given these figures, a Chennai-based study on the economic burden of diabetes care is important.

This study has achieved its objective of assessing the cost of diabetes care with a specific focus on middle-aged and middle-income groups and provides significant insight, as detailed in the discussion section. A suggested next step might be to increase the study population size and expand to northern part of the city. This could help build a large model based on the economic burden of diabetes care for the people living in the city of Chennai.

Acknowledgement

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World Health Organization

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Diabetes: the cost of diabetes

Fact sheet N°236

As the number of people with diabetes grows worldwide, the disease takes an ever-increasing proportion of national health care budgets. Without primary prevention, the diabetes epidemic will continue to grow. Even worse, diabetes is projected to become one of the world's main disablers and killers within the next twenty-five years. Immediate action is needed to stem the tide of diabetes and to introduce cost-effective treatment strategies to reverse this trend.

Diabetes: the size of the problem

A diabetes epidemic is underway. An estimated 30 million people world-wide had diabetes in 1985. By 1995, this number had shot up to 135 million. The latest WHO estimate (for the number of people with diabetes, world-wide, in 2000) is 177 million. This will increase to at least 300 million by 2025. The number of deaths attributed to diabetes was previously estimated at just over 800,000. However, it has long been known that the number of deaths related to diabetes is considerably underestimated. A more plausible figure is likely to be around 4 million deaths per year related to the presence of the disorder. This is about 9% of the global total. Many of these diabetes related deaths are from cardiovascular complications. Most of them are premature deaths when the people concerned are economically contributing to society. This situation is increasingly outstretching the health-care resources devoted to diabetes.

For WHO and the International Diabetes Federation (IDF), sponsors of World Diabetes Day, this increase can and must be prevented with the right measures.

What are the costs of diabetes?

- Because of its chronic nature, the severity of its complications and the means required to control them, diabetes is a costly disease, not only for the affected individual and his/her family, but also for the health authorities.
- Studies in India estimate that, for a low-income Indian family with an adult with diabetes, as much as 25% of family income may be devoted to diabetes care. For families in the USA with a child who has diabetes, the corresponding figure is 10%.
- The total health care costs of a person with diabetes in the USA are between twice and three times those for people without the condition. It was calculated, for example, that the cost of treating diabetes in the USA in 1997 was US$ 44 billion.
- In WHO's Western Pacific region a recent analysis of health care expenditure has shown that: 16% of hospital expenditure was on

people with diabetes. In the Republic of the Marshall Islands, this figure was 25%. 20% of "offshore expenditure" on health by Fiji was on diabetes related complications – instances where facilities for care were not available in Fiji, so patients had to travel elsewhere. These represent considerable sums for countries who can ill afford such massive expenditure on preventable conditions. The costs of diabetes affect everyone, everywhere, but they are not only a financial problem. Intangible costs (pain, anxiety, inconvenience and generally lower quality of life etc.) also have great impact on the lives of patients and their families and are the most difficult to quantify.

- The costs of diabetes affect everyone, everywhere, but they are not only a financial problem. Intangible costs (pain, anxiety, inconvenience and generally lower quality of life etc.) also have great impact on the lives of patients and their families and are the most difficult to quantify.

Direct costs:

- Direct costs to individuals and their families include medical care, drugs, insulin and other supplies. Patients may also have to bear other personal costs, such as increased payments for health, life and automobile insurance.
- Direct costs to the healthcare sector include hospital services, physician services, lab tests and the daily management of diabetes – which includes availability of products such as insulin, syringes, oral hypoglycaemic agents and blood-testing equipment. Costs range from relatively low-cost items, such as primary-care consultations and hospital outpatient episodes, to very high-cost items, such as long hospital inpatient stays for the treatment of complications.
- Recent cost estimates, denied by similar methods to that quoted above for the USA, include those for Brazil (US$ 3.9 billion), Argentina (US$ 0.8 billion) and Mexico (US$ 2.0 billion). Each of these is an annual figure and is rising as diabetes prevalence increases. Overall, direct health care costs of diabetes range from 2.5% to 15% annual health care budgets, depending on local diabetes prevalence and the sophistication of the treatment available.
- For most countries, the largest single item of diabetes expenditure is hospital admissions for the treatment of long-term complications, such as heart disease and stroke, kidney failure and foot problems. Many of those are potentially preventable given prompt diagnosis of diabetes, effective patient and professional education and comprehensive long term care.

Costs of lost production ("indirect costs")

- A number of diabetes patients may not be able to continue working or work as effectively as they could before the onset of their condition.
- Sickness, absence, disability, premature retirement or premature mortality can cause loss of productivity.
- Estimating the cost to society of this loss of productivity is not easy. However, in many cases where estimates have been made, these costs of lost production may be as great or even greater than direct health care costs. For example, the US estimate of direct costs of US$ 44 billion mentioned above needs to be set against an estimated US$ 54 billion of loss of productivity during the same year (1997). Combining the cost estimates for 25 Latin American countries suggests that costs of lost production may be as much as five times the direct health care cost. This may be because there is limited access to high quality care with, consequently, a high incidence of complications, disability and premature mortality. Families too, of course, suffer loss of earnings as a result of diabetes and its consequences.

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Intangible costs

- Pain, anxiety, inconvenience and other factors which decrease quality of life are intangible costs, which are just as heavy. Some activities may have to be foregone in favour of treatment, discrimination may be experienced in the workplace, obtaining jobs may be more difficult, and professional life may be shortened because of complications leading to early disability and even death.
- Personal relationships, leisure and mobility can also be negatively influenced. Diabetes treatment, particularly insulin injection and self-monitoring, can be time-consuming, inconvenient and uncomfortable.

Prevention and diabetes:

Effective prevention also means more cost-effective healthcare. This may be the prevention of the onset of diabetes itself (primary prevention) or the prevention of its immediate and longer-term consequences (secondary prevention).

- Primary prevention protects susceptible individuals from developing diabetes. It has an impact by reducing or delaying both the need for diabetes care and the need to treat diabetes complications. Reliable examples of this measure come from studies undertaken among susceptible groups in China. Lifestyle modifications (appropriate diet and increased physical activity and a consequent reduction of weight), supported by a continuous education programme, were used to achieve a reduction of almost two-thirds in the progression to diabetes over a six-year period. This type of measure is not easy, but is likely to be cost effective if it can be implemented on a population scale. It should be considered particularly in the poorest regions of the world where resources are severely limited. Similar results have also been achieved recently in Finland and the USA.
- Such preventive measures will have benefits above and beyond diabetes since improvements in diet and day-to-day physical activity will reduce obesity, cardiovascular disease and some cancers.

Secondary prevention includes early detection, prevention and treatment. Appropriate action taken at the right time is beneficial in terms of quality of life, and is cost-effective, especially if it can prevent hospital admission.

Secondary prevention measures:

- The treatment of high blood pressure and raised blood lipids, as well as the control of blood glucose levels, can substantially reduce the risk of developing complications and slow their progression in all types of diabetes.
- Another cost-saving strategy is the prevention of foot ulceration and amputation. Effective foot-care reduces both the frequency and length of hospital stays and the incidence of amputation in diabetes patients by as much as 50%.
- Screening and early treatment for retinopathy is also very cost-effective, given the devastating direct, indirect and intangible costs of blindness.
- Screening for protein in urine is another valid preventive measure to prevent or slow down the inevitable progression to kidney failure. Furthermore, there is evidence that screening for traces of protein is cost saving, as it allows even earlier intervention in the natural course of kidney disease.
- Measures to reduce the consumption of tobacco will also assist in the management of diabetes. Cigarette smoking has been found to

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be associated with poor control of blood glucose and it is also strongly causally related to hypertension and heart disease in people with diabetes as well as those without.

WHO and IDF are committed to working for access to high quality health care for people with diabetes wherever they live and for primary prevention to reduce the impact of diabetes and its complications in the future.

For more information contact:

WHO Media centre
Telephone: +41 22 791 2222
E-mail: mediainquiries@who.int

Related links

Diabetes

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ANNEXURE - L

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONGLYZA safely and effectively. See full prescribing information for ONGLYZA.

ONGLYZA (saxagliptin) tablets, for oral use

Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

ONGLYZA is a dipeptidyl peptidase-4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. (1.1, 14)

Limitations of Use:

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.2)
- Has not been studied in patients with a history of pancreatitis (1.2, 5.1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)
- Patients with moderate or severe renal impairment, or end-stage renal disease (CrCl ≤50 mL/min): Recommended dosage is 2.5 mg once daily regardless of meals. (2.2)
- Assess renal function before starting ONGLYZA and periodically thereafter. (2.2)
- 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole). (2.3, 7.1)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 5 mg and 2.5 mg (3)

----------CONTRAINDICATIONS----------

- History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to ONGLYZA. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Acute Pancreatitis (postmarketing reports):* If pancreatitis is suspected, promptly discontinue ONGLYZA (saxagliptin). (5.1)
- *Hypoglycemia:* In add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was more common in patients treated with ONGLYZA compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.2, 6.1)
- *Hypersensitivity-Related Events (e.g., urticaria, facial edema):* More common in patients treated with ONGLYZA than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. Promptly discontinue ONGLYZA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.3, 6.1, 6.2)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug. (5.4)

----------ADVERSE REACTIONS----------

- *Adverse reactions reported in ≥5% of patients treated with ONGLYZA and more* commonly than in patients treated with placebo are upper respiratory tract infection, urinary tract infection, and headache. (6.1)
- Peripheral edema was reported more commonly in patients treated with the combination of ONGLYZA and a thiazolidinedione (TZD) than in patients treated with the combination of placebo and TZD. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------

- *Strong CYP3A4/5 inhibitors (e.g., ketoconazole):* Coadministration with ONGLYZA significantly increases saxagliptin concentrations. Recommend limiting ONGLYZA dosage to 2.5 mg once daily. (2.3, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- No adequate and well-controlled studies in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. [See *Clinical Studies (14)*.]

1.2 Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using ONGLYZA. [See *Warnings and Precautions (5.1)*.]

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals.

ONGLYZA tablets must not be split or cut.

2.2 Dosage in Patients with Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min).

The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min) [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)*]. ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dosage of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease formula. [See *Clinical Pharmacology (12.3)*.]

2.3 Dosage Adjustment with Concomitant Use of Strong CYP3A4/5 Inhibitors

The dosage of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). [See *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*.]

2.4 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When ONGLYZA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. [See *Warnings and Precautions (5.2)*.]

3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the reverse side, in blue ink.
- ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction to ONGLYZA, such as anaphylaxis, angioedema, or exfoliative skin conditions. [See *Warnings and Precautions (5.3)* and *Adverse Reactions (6.2)*.]

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. After initiation of ONGLYZA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ONGLYZA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

5.2 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

When ONGLYZA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. [See *Adverse Reactions (6.1)*.] Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with ONGLYZA. [See *Dosage and Administration (2.4)*.]

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2)*.]

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with ONGLYZA.

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions with Monotherapy and with Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin. The 10 mg dosage is not an approved dosage.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	Placebo N=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10 mg dosage is not an approved dosage. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of ONGLYZA on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Adverse Reactions in Patients with Renal Impairment

ONGLYZA 2.5 mg was compared to placebo in a 12-week trial in 170 patients with type 2 diabetes and moderate or severe renal impairment or end-stage renal disease (ESRD). The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo.

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [see *Clinical Studies (14.2)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo, except for confirmed hypoglycemia [see *Adverse Reactions (6.1)*].

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Adverse Reactions with Concomitant Use with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Table 2: Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

	Number (%) of Patients	
	ONGLYZA 5 mg + Metformin* N=320	Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo [see *Warnings and Precautions (5.2)*]. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4% in patients given metformin alone.

In the active-controlled trial comparing add-on therapy with ONGLYZA 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with ONGLYZA 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the *ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) ($p<0.0001$).*

During 12 weeks of treatment in patients with moderate or severe renal impairment or ESRD, the overall incidence of reported hypoglycemia was 20% among patients treated with ONGLYZA 2.5 mg and 22% among patients treated with placebo. Four ONGLYZA-treated patients (4.7%) and three placebo-treated patients (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

In the add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for ONGLYZA 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was higher with ONGLYZA 5 mg (5.3%) versus placebo (3.3%).

In the add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for ONGLYZA 5 mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the ONGLYZA-treated patients and in none of the placebo-treated patients [see *Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One ONGLYZA-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Infections

In the unblinded, controlled, clinical trial database for ONGLYZA to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 ONGLYZA-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with ONGLYZA until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of ONGLYZA that remained stable throughout ONGLYZA treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with ONGLYZA use. Causality has not been estimated and there are too few cases to date to determine whether tuberculosis is related to ONGLYZA use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in an ONGLYZA-treated patient who developed

suspected foodborne fatal salmonella sepsis after approximately 600 days of ONGLYZA therapy. There have been no spontaneous reports of opportunistic infections associated with ONGLYZA use.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the ONGLYZA 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The 10 mg dosage is not an approved dosage.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of ONGLYZA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications (4)* and *Warnings and Precautions (5.3)*.]
- Acute pancreatitis. [See *Indications and Usage (1.2)* and *Warnings and Precautions (5.1)*.]

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the MRHD (saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

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8.3 Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of ONGLYZA in pediatric patients have not been performed.

8.5 Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*.]

10 OVERDOSAGE

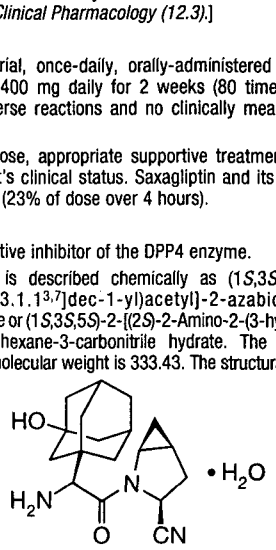
In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7.1)*.]

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group) compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

The degree of renal impairment did not affect the C_{max} of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The 10 mg dosage is not an approved dosage. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.

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Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

In Vivo Assessment of Drug Interactions

Table 3: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin 5-hydroxy saxagliptin	2.09 0.66	1.63 0.57
Rifampin§	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39

(Continued)

Table 3: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin *(Continued)*

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
Limit ONGLYZA dose to 2.5 mg once daily when coadministered with strong CYP3A4/5 inhibitors [see *Drug Interactions (7.1)* and *Dosage and Administration (2.3)*]:					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* Single dose unless otherwise noted.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.
‡ Results exclude one subject.
§ The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin.
ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

Table 4: Effect of Saxagliptin on Systemic Exposures of Coadministered *Drugs*

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	1.06	1.09
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol and Norgestimate	ethinyl estradiol 0.035 mg and norgestimate 0.250 mg for 21 days	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	1.07 1.10 1.13	0.98 1.09 1.17

* Single dose unless otherwise noted. † AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses. ‡ Results include all subjects. ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Mutagenesis

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Impairment of Fertility

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

13.2 Animal Toxicology and/or Pharmacology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated a saxagliptin dose of 10 mg daily. The 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. The 10 mg dosage is not an approved dosage. Treatment with ONGLYZA 5 mg and 2.5 mg doses produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

ONGLYZA has also been evaluated in four additional trials in patients with type 2 diabetes: an active-controlled trial comparing add-on therapy with ONGLYZA to glipizide in 858 patients inadequately controlled on metformin alone, a trial comparing ONGLYZA to placebo in 455 patients inadequately controlled on insulin alone or on insulin in combination with metformin, a trial comparing ONGLYZA to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea, and a trial comparing ONGLYZA to placebo in 170 patients with type 2 diabetes and moderate or severe renal impairment or ESRD.

14.1 Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C ≥7% to ≤10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. The 10 mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 5). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group.

ONGLYZA® (saxagliptin)

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	*ONGLYZA 2.5 mg* N=102	*ONGLYZA 5 mg* N=106	*Placebo* N=95
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	−0.4	−0.5	+0.2
Difference from placebo (adjusted mean†)	−0.6‡	−0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
***2-hour Postprandial Glucose* (mg/dL)**	***N=78***	***N=84***	***N=71***
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo
§ p-value <0.05 compared to placebo
¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA.

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of −0.4% and −0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of −0.4%).

14.2 Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. The 10 mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 6). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

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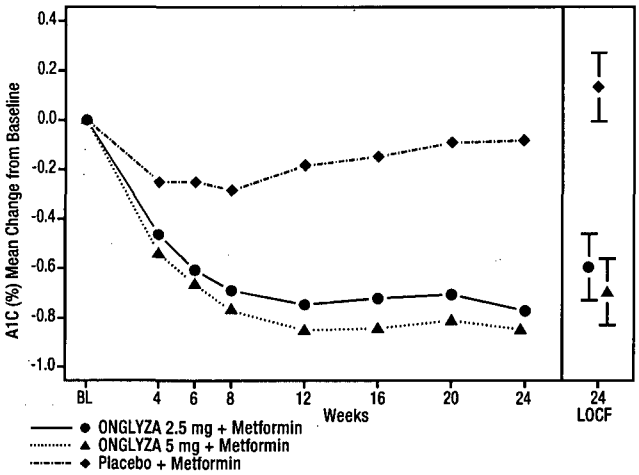
Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	ONGLYZA 2.5 mg + Metformin N=192	ONGLYZA 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

Figure 1: Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin*



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 7). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA 2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 2.5 mg + TZD N=195	ONGLYZA 5 mg + TZD N=186	Placebo + TZD N=184
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.4§	−0.6‡	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%§ (81/192)	42%§ (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean†)	−14	−17	−3
Difference from placebo (adjusted mean†)	−12§	−15§	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean†)	−55	−65	−15
Difference from placebo (adjusted mean†)	−40§	−50§	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + TZD
§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 8). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

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Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248	ONGLYZA 5 mg + Glyburide 7.5 mg N=253	Placebo + Up-Titrated Glyburide N=267
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean†)	−0.5	−0.6	+0.1
Difference from up-titrated glyburide (adjusted mean†)	−0.6‡	−0.7‡	
95% Confidence Interval	(−0.8, −0.5)	(−0.9, −0.6)	
Percent of patients achieving A1C <7%	22%§ (55/246)	23%§ (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean†)	−7	−10	+1
Difference from up-titrated glyburide (adjusted mean†)	−8§	−10§	
95% Confidence Interval	(−14, −1)	(−17, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean†)	−31	−34	+8
Difference from up-titrated glyburide (adjusted mean†)	−38§	−42§	
95% Confidence Interval	(−50, −27)	(−53, −31)	

*Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + up-titrated glyburide
§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, active-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. The 10 mg dosage is not an approved dosage. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 9).

Table 9: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	

(Continued)

Table 9: (Continued) Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−41§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

Add-On Combination Therapy with Metformin versus Glipizide Add-On Combination Therapy with Metformin

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin alone were randomized to double-blind add-on therapy with ONGLYZA or glipizide. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks prior to enrollment.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin (1500-3000 mg based on their pre-study dose). Following the lead-in period, eligible patients were randomized to 5 mg of ONGLYZA or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, ONGLYZA and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin therapy (Table 10). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with ONGLYZA compared to a mean weight gain of 1.1 kg in patients treated with glipizide (p<0.0001).

Table 10: Glycemic Parameters at Week 52 in an Active-Controlled Trial of ONGLYZA versus Glipizide in Combination with Metformin*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=428	Titrated Glipizide + Metformin N=430
Hemoglobin A1C (%)	**N=423**	**N=423**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean†)	−0.6	−0.7
Difference from glipizide + metformin (adjusted mean†)	0.1	
95% Confidence Interval	(−0.02, 0.2)‡	
Fasting Plasma Glucose (mg/dL)	**N=420**	**N=420**
Baseline (mean)	162	161
Change from baseline (adjusted mean†)	−9	−16
Difference from glipizide + metformin (adjusted mean†)	6	
95% Confidence Interval	(2, 11)§	

* Intent-to-treat population using last observation on study.
† Least squares mean adjusted for baseline value.
‡ ONGLYZA + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%.
§ Significance not tested.

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Add-On Combination Therapy with Insulin (with or without metformin)

A total of 455 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either ONGLYZA 5 mg or placebo. Doses of the antidiabetic therapies were to remain stable but patients were rescued and allowed to adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with ONGLYZA 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 11). Similar mean reductions in A1C versus placebo were observed for patients using ONGLYZA 5 mg add-on to insulin alone and ONGLYZA 5 mg add-on to insulin in combination with metformin (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the ONGLYZA group and 32% in the placebo group.

The mean daily insulin dose at baseline was 53 units in patients treated with ONGLYZA 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the ONGLYZA 5 mg group and 5 units for the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Insulin*

Efficacy Parameter	ONGLYZA 5 mg + Insulin (+/− Metformin) N=304	Placebo + Insulin (+/− Metformin) N=151
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean†)	−0.7	−0.3
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	**N=262**	**N=129**
Baseline (mean)	251	255
Change from baseline (adjusted mean†)	−27	−4
Difference from placebo (adjusted mean†)	−23§	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value and metformin use at baseline.
‡ p-value <0.0001 compared to placebo + insulin
§ p-value <0.05 compared to placebo + insulin

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 17% (52/300) with ONGLYZA in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin plus a sulfonylurea in patients with inadequate glycemic control (A1C ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind ONGLYZA (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

ONGLYZA in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 12). The percentage of patients who discontinued for lack of glycemic control was 6% in the ONGLYZA group and 5% in the placebo group.

Table 12: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129	Placebo + Metformin plus Sulfonylurea N=128
Hemoglobin A1C (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.5)	
2-hour Postprandial Glucose (mg/dL)	**N=115**	**N=113**
Baseline (mean)	268	262
Change from baseline (adjusted mean†)	−12	5
Difference from placebo (adjusted mean†)	−17§	
95% Confidence Interval	(−32, −2)	

* Intent-to-treat population using last observation prior to discontinuation.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin plus sulfonylurea
§ p-value <0.05 compared to placebo + metformin plus sulfonylurea

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with ONGLYZA in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

14.3 Renal Impairment

A total of 170 patients participated in a 12-week, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of ONGLYZA 2.5 mg once daily compared with placebo in patients with type 2 diabetes and moderate (n=90) or severe (n=41) renal impairment or ESRD (n=39). In this trial, 98% of the patients were using background antidiabetic medications (75% were using insulin and 31% were using oral antidiabetic medications, mostly sulfonylureas).

After 12 weeks of treatment, ONGLYZA 2.5 mg provided significant improvement in A1C compared to placebo (Table 13). In the subgroup of patients with ESRD, ONGLYZA and placebo resulted in comparable reductions in A1C from baseline to Week 12. This finding is inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

After 12 weeks of treatment, the mean change in FPG was −12 mg/dL with ONGLYZA 2.5 mg and −13 mg/dL with placebo. Compared to placebo, the mean change in FPG with ONGLYZA was −12 mg/dL in the subgroup of patients with moderate renal impairment, −4 mg/dL in the subgroup of patients with severe renal impairment, and +44 mg/dL in the subgroup of patients with ESRD. These findings are inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

Table 13: A1C at Week 12 in a Placebo-Controlled Trial of ONGLYZA in Patients with Renal Impairment*

Efficacy Parameter	ONGLYZA 2.5 mg N=85	Placebo N=85
Hemoglobin A1C (%)	**N=81**	**N=83**
Baseline (mean)	8.4	8.1
Change from baseline (adjusted mean†)	−0.9	−0.4
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.7, −0.1)	

* Intent-to-treat population using last observation on study.
† Least squares mean adjusted for baseline value.
‡ p-value <0.01 compared to placebo

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA® (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 14.

Table 14: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	pink biconvex, round	"5" on one side and "4215" on the reverse, in blue ink	Bottles of 30	0003-4215-11
			Bottles of 90	0003-4215-21
			Bottles of 500	0003-4215-31
			Blister of 100	0003-4215-41
2.5 mg	pale yellow to light yellow biconvex, round	"2.5" on one side and "4214" on the reverse, in blue ink	Bottles of 30	0003-4214-11
			Bottles of 90	0003-4214-21

Storage and Handling

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Medication Guide

Healthcare providers should instruct their patients to read the Medication Guide before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Pancreatitis

Patients should be informed that acute pancreatitis has been reported during postmarketing use of ONGLYZA. Before initiating ONGLYZA, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue ONGLYZA and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.1)*].

Hypersensitivity Reactions

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during postmarketing use of ONGLYZA. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking ONGLYZA and seek medical advice promptly.

Missed Dose

Patients should be informed that if they miss a dose of ONGLYZA they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

Administration Instructions

Patients should be informed that ONGLYZA tablets must not be split or cut.

Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1297954A0 / 1256314A4

MEDICATION GUIDE

ONGLYZA (on-GLY-zah) (saxagliptin) tablets

Read this Medication Guide carefully before you start taking ONGLYZA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have any questions about ONGLYZA, ask your healthcare provider.

What is the most important information I should know about ONGLYZA?

Serious side effects can happen to people taking ONGLYZA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking ONGLYZA:

Tell your healthcare provider if you have ever had

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with ONGLYZA.

Stop taking ONGLYZA and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is ONGLYZA?

- ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.
- ONGLYZA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low. However, hypoglycemia may still occur with ONGLYZA. Your risk for getting hypoglycemia is higher if you take ONGLYZA with some other diabetes medicines, such as a sulfonylurea or insulin.

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- ONGLYZA is not for people with type 1 diabetes.
- ONGLYZA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take ONGLYZA.

It is not known if ONGLYZA is safe and effective in children younger than 18 years old.

Who should not take ONGLYZA?

Do not take ONGLYZA if you:

- are allergic to any ingredients in ONGLYZA. See the end of this Medication Guide for a complete list of ingredients in ONGLYZA.

  Symptoms of a serious allergic reaction to ONGLYZA may include:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

What should I tell my healthcare provider before taking ONGLYZA?

Before you take ONGLYZA, tell your healthcare provider if you:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as

ONGLYZA® (saxagliptin)

antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- Do not split or cut ONGLYZA tablets.
- During periods of stress on the body, such as:
  - fever
  - trauma
  - infection
  - surgery

  Contact your healthcare provider right away as your medication needs may change.
- Your healthcare provider should test your blood to measure how well your kidneys are working before and during your treatment with ONGLYZA. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?

ONGLYZA can cause serious side effects, including:

- See "**What is the most important information I should know about ONGLYZA?**"
- **Allergic (hypersensitivity) reactions**, such as:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

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- skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68°F and 77°F (20°C and 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals. For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

ONGLYZA® (saxagliptin)

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ONGLYZA (saxagliptin) tablets

Manufactured by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:

Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Bristol-Myers Squibb

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ANNEXURE-M

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Bristol-Myers Squibb Company AstraZeneca

PACKAGE LEAFLET TEXT

Kombiglyze™ XR

(saxagliptin/metformin HCl extended-release)

Tablets 2.5mg/1000mg, 5mg/500mg, 5mg/1000mg

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately. [See *Warnings and Precautions (5.1)*.]

1 INDICATIONS AND USAGE

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on saxagliptin or metformin alone, or in patients already being treated with the combination of saxagliptin and metformin. [See *Clinical Studies (13)*.]

1.1 Limitations of Use

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using KOMBIGLYZE XR. [See *Warnings and Precautions (5.2)*.]

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2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The dosage of KOMBIGLYZE XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability. KOMBIGLYZE XR should generally be administered once daily with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin. The following dosage forms are available:

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 5 mg/500 mg
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 5 mg/1000 mg
- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets 2.5 mg/1000 mg

The recommended starting dose of KOMBIGLYZE XR in patients who need 5 mg of saxagliptin and who are not currently treated with metformin is 5 mg saxagliptin/500 mg metformin extended-release once daily with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dosage of KOMBIGLYZE XR should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose. Following a switch from metformin immediate-release to metformin extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly.

Patients who need 2.5 mg saxagliptin in combination with metformin extended-release may be treated with KOMBIGLYZE XR 2.5 mg/1000 mg. Patients who need 2.5 mg saxagliptin who are either metformin naive or who require a dose of metformin higher than 1000 mg should use the individual components.

The maximum daily recommended dosage is 5 mg for saxagliptin and 2000 mg for metformin extended-release.

No studies have been performed specifically examining the safety and efficacy of KOMBIGLYZE XR in patients previously treated with other antihyperglycemic medications and switched to KOMBIGLYZE XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

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Inform patients that KOMBIGLYZE XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of KOMBIGLYZE XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

2.2 Dosage Adjustments with Concomitant Use of Strong CYP3A4/5 Inhibitors

The maximum recommended dosage of saxagliptin is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). For these patients, limit the KOMBIGLYZE XR dosage to 2.5 mg/1000 mg once daily. [See *Dosage and Administration (2.1)*, *Drug Interactions (7.1)*, and *Clinical Pharmacology (11.3)*.]

2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When KOMBIGLYZE XR is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dosage of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. [See *Warnings and Precautions (5.9)*.]

3 DOSAGE FORMS AND STRENGTHS

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 5 mg/500 mg tablets are light brown to brown, biconvex, capsule-shaped, film-coated tablets with "5/500" printed on one side and "4221" printed on the reverse side, in blue ink.

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 5 mg/1000 mg tablets are pink, biconvex, capsule-shaped, film-coated tablets with "5/1000" printed on one side and "4223" printed on the reverse side, in blue ink.

- KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) 2.5 mg/1000 mg tablets are pale yellow to light yellow, biconvex, capsule-shaped, film-coated tablets with "2.5/1000" printed on one side and "4222" printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

KOMBIGLYZE XR is contraindicated in patients with:

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- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.

- Hypersensitivity to metformin hydrochloride.

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

- History of a serious hypersensitivity reaction to KOMBIGLYZE XR or saxagliptin, such as anaphylaxis, angioedema, or exfoliative skin conditions, or to any of the ingredients of this product. [See *Warnings and Precautions (5.13)* and *Adverse Reactions (6.2)*.]

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with KOMBIGLYZE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal

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function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [see *Warnings and Precautions (5.3, 5.6, 5.7, 5.11)*].

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur [see *Warnings and Precautions (5.12)*]. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal, but less than 5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. [See *Warnings and Precautions (5.8)*.]

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery [see *Contraindications (4)* and *Warnings and Precautions (5.6, 5.7, 5.10, 5.11, 5.12)*].

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5.2 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking saxagliptin. After initiation of KOMBIGLYZE XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, KOMBIGLYZE XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using KOMBIGLYZE XR.

5.3 Assessment of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, KOMBIGLYZE XR is contraindicated in patients with renal impairment [see *Contraindications (4)*].

Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and KOMBIGLYZE XR discontinued if evidence of renal impairment is present.

5.4 Impaired Hepatic Function

Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, KOMBIGLYZE XR is not recommended in patients with hepatic impairment.

5.5 Vitamin B_{12} Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE XR and any apparent abnormalities should be appropriately investigated and managed [see *Adverse Reactions (6.1)*].

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Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

5.6 Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving KOMBIGLYZE XR.

5.7 Surgical Procedures

Use of KOMBIGLYZE XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

5.8 Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well controlled on KOMBIGLYZE XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, KOMBIGLYZE XR must be stopped immediately and other appropriate corrective measures initiated.

5.9 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

Saxagliptin

When saxagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. [See *Adverse Reactions (6.1)*.] Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with KOMBIGLYZE XR. [See *Dosage and Administration (2.3)*.]

Metformin hydrochloride

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Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

5.10 Concomitant Medications Affecting Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion [see *Drug Interactions (7.2)*], should be used with caution.

5.11 Radiologic Studies with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

5.12 Hypoxic States

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on KOMBIGLYZE XR therapy, the drug should be promptly discontinued.

5.13 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with saxagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with saxagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2)*.]

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Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with KOMBIGLYZE XR.

5.14 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions with Monotherapy and with Add-On Combination Therapy

Metformin hydrochloride

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Saxagliptin

In two placebo-controlled monotherapy trials of 24-week duration, patients were treated with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin immediate-release, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin immediate-release. The 10 mg saxagliptin dosage is not an approved dosage.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin immediate-release trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse

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events in patients treated with saxagliptin 2.5 mg and saxagliptin 5 mg was similar to placebo (72% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with saxagliptin 2.5 mg or at least 2 patients treated with saxagliptin 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with saxagliptin 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with Saxagliptin 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	Saxagliptin 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with saxagliptin 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with saxagliptin 2.5 mg or saxagliptin 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for saxagliptin (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10 mg saxagliptin dosage is not an approved dosage. The incidence rate of fracture events in patients who received saxagliptin did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

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An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to saxagliptin is not known.

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [see *Clinical Studies (13.4)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between saxagliptin and placebo, except for confirmed hypoglycemia [see **Hypoglycemia** subsection *Adverse Reactions (6.1)*].

Adverse Reactions Associated with Saxagliptin Coadministered with Metformin Immediate-Release in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered saxagliptin and metformin in treatment-naive patients.

Table 2: Coadministration of Saxagliptin and Metformin Immediate-Release in Treatment-Naive Patients: Adverse Reactions Reported in ≥5% of Patients Treated with Combination Therapy of Saxagliptin 5 mg Plus Metformin Immediate-Release (and More Commonly than in Patients Treated with Metformin Immediate-Release Alone)

	Number (%) of Patients	
	Saxagliptin 5 mg + Metformin* N=320	**Placebo + Metformin* N=328**
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin immediate-release was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

In patients treated with the combination of saxagliptin and metformin immediate-release, either as saxagliptin add-on to metformin immediate-release therapy or as coadministration in treatment-naive patients, diarrhea was the only gastrointestinal-related event that occurred with an incidence ≥5% in any treatment group in both studies. In the saxagliptin add-on to metformin immediate-release trial, the incidence of diarrhea was 9.9%, 5.8%, and 11.2% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of diarrhea was 6.9% in the saxagliptin 5 mg + metformin immediate-release group and 7.3% in the placebo + metformin immediate-release group.

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Hypoglycemia

In the saxagliptin clinical trials, adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

The incidence of reported hypoglycemia for saxagliptin 2.5 mg and saxagliptin 5 mg versus placebo given as monotherapy was 4% and 5.6% versus 4.1%, respectively. In the add-on to metformin immediate-release trial, the incidence of reported hypoglycemia was 7.8% with saxagliptin 2.5 mg, 5.8% with saxagliptin 5 mg, and 5% with placebo. When saxagliptin and metformin immediate-release were coadministered in treatment-naive patients, the incidence of reported hypoglycemia was 3.4% in patients given saxagliptin 5 mg + metformin immediate-release and 4% in patients given placebo + metformin immediate-release.

In the active-controlled trial comparing add-on therapy with saxagliptin 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with saxagliptin 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the saxagliptin-treated patients and in 35 glipizide-treated patients (8.1%) ($p<0.0001$).

In the saxagliptin add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for saxagliptin 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was higher with saxagliptin 5 mg (5.3%) versus placebo (3.3%). Among the patients using insulin in combination with metformin, the incidence of confirmed symptomatic hypoglycemia was 4.8% with saxagliptin versus 1.9% with placebo.

In the saxagliptin add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for saxagliptin 5 mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the saxagliptin-treated patients and in none of the placebo-treated patients [see *Warnings and Precautions (5.9)*].

Hypersensitivity Reactions

Saxagliptin

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received saxagliptin

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2.5 mg, saxagliptin 5 mg, and placebo, respectively. None of these events in patients who received saxagliptin required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Infections

Saxagliptin

In the unblinded, controlled, clinical trial database for saxagliptin to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 saxagliptin-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with saxagliptin use. Causality has not been established and there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. There have been no spontaneous reports of opportunistic infections associated with saxagliptin use.

Vital Signs

Saxagliptin

No clinically meaningful changes in vital signs have been observed in patients treated with saxagliptin alone or in combination with metformin.

Laboratory Tests

Absolute Lymphocyte Counts

Saxagliptin

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There was a dose-related mean decrease in absolute lymphocyte count observed with saxagliptin. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with saxagliptin 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when saxagliptin 5 mg and metformin were coadministered in treatment-naive patients compared to placebo and metformin. There was no difference observed for saxagliptin 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to saxagliptin although some patients had recurrent decreases upon rechallenge that led to discontinuation of saxagliptin. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The 10 mg saxagliptin dosage is not an approved dosage.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of saxagliptin on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Vitamin B_{12} Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KOMBIGLYZE XR and any apparent abnormalities should be appropriately investigated and managed. [See *Warnings and Precautions (5.5)*.]

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of saxagliptin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications (4)* and *Warnings and Precautions (5.13)*.]
- Acute pancreatitis. [See *Indications and Usage (1.1)* and *Warnings and Precautions (5.2)*.]

7 DRUG INTERACTIONS

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7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Saxagliptin

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of saxagliptin should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (11.3).*]

7.2 Cationic Drugs

Metformin hydrochloride

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in healthy volunteers. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of KOMBIGLYZE XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

7.3 Use with Other Drugs

Metformin hydrochloride

Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving KOMBIGLYZE XR, the patient should be closely observed for loss of glycemic control. When such drugs are withdrawn from a patient receiving KOMBIGLYZE XR, the patient should be observed closely for hypoglycemia.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women with KOMBIGLYZE XR or its individual components. Because animal reproduction studies are not always predictive of human response, KOMBIGLYZE XR, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (MRHD; saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the MRHD of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

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Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Nursing Mothers

No studies in lactating animals have been conducted with the combined components of KOMBIGLYZE XR. In studies performed with the individual components, both saxagliptin and metformin are secreted in the milk of lactating rats. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.

8.3 Pediatric Use

Safety and effectiveness of KOMBIGLYZE XR in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of KOMBIGLYZE XR in pediatric patients have not been performed.

8.4 Geriatric Use

KOMBIGLYZE XR

Elderly patients are more likely to have decreased renal function. Because metformin is contraindicated in patients with renal impairment, carefully monitor renal function in the elderly and use KOMBIGLYZE XR with caution as age increases. [See *Warnings and Precautions (5.1, 5.3)* and *Clinical Pharmacology (11.3).*]

Saxagliptin

In the six, double-blind, controlled clinical safety and efficacy trials of saxagliptin, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

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Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney. Because the risk of lactic acidosis with metformin is greater in patients with impaired renal function, KOMBIGLYZE XR should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. [See *Contraindications (4)*, *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (11.3)*.]

9 OVERDOSAGE

Saxagliptin

In a controlled clinical trial, once-daily, orally-administered saxagliptin in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

10 DESCRIPTION

KOMBIGLYZE XR (saxagliptin and metformin HCl extended-release) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: saxagliptin and metformin hydrochloride.

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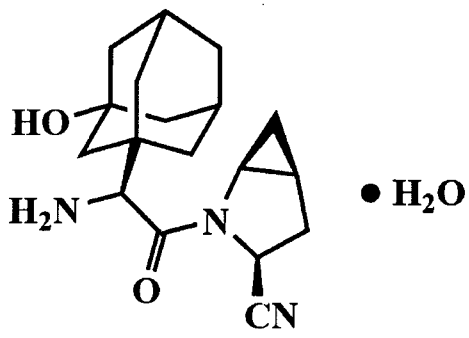
Saxagliptin

Saxagliptin is an orally-active inhibitor of the dipeptidyl-peptidase-4 (DPP4) enzyme.

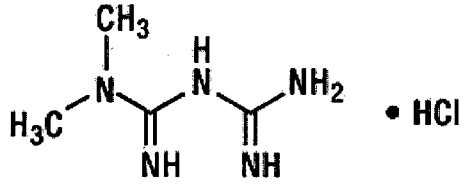
Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



KOMBIGLYZE XR

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KOMBIGLYZE XR is available for oral administration as tablets containing either 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and 500 mg metformin hydrochloride (KOMBIGLYZE XR 5 mg/500 mg), or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and 1000 mg metformin hydrochloride (KOMBIGLYZE XR 5 mg/1000 mg), or 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin and 1000 mg metformin hydrochloride (KOMBIGLYZE XR 2.5 mg/1000 mg). Each film-coated tablet of KOMBIGLYZE XR contains the following inactive ingredients: carboxymethylcellulose sodium, hypromellose 2208, and magnesium stearate. The 5 mg/500 mg strength tablet of KOMBIGLYZE XR also contains microcrystalline cellulose and hypromellose 2910. In addition, the film coatings contain the following inactive ingredients: polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, and iron oxides.

The biologically inert components of the tablet may occasionally remain intact during gastrointestinal transit and will be eliminated in the feces as a soft, hydrated mass.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

KOMBIGLYZE XR

KOMBIGLYZE XR combines two antihyperglycemic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes: saxagliptin, a dipeptidyl-peptidase-4 (DPP4) inhibitor, and metformin hydrochloride, a biguanide.

Saxagliptin

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

Metformin hydrochloride

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Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in unusual circumstances [see *Warnings and Precautions (5.9)*] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

11.2 Pharmacodynamics

Saxagliptin

In patients with type 2 diabetes mellitus, administration of saxagliptin inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

Saxagliptin

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, saxagliptin was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

11.3 Pharmacokinetics

KOMBIGLYZE XR

Bioequivalence and food effect of KOMBIGLYZE XR was characterized under low calorie diet. The low calorie diet consisted of 324 kcal with meal composition that contained 11.1% protein, 10.5% fat, and 78.4% carbohydrate. The results of bioequivalence studies in healthy subjects demonstrated that KOMBIGLYZE XR combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin (ONGLYZA®) and metformin hydrochloride extended-release as individual tablets under fed conditions.

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Saxagliptin

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Metformin hydrochloride

Metformin extended-release C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg. After repeated administration of metformin extended-release, metformin did not accumulate in plasma. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. Peak plasma levels of metformin extended-release tablets are approximately 20% lower compared to the same dose of metformin immediate-release tablets, however, the extent of absorption (as measured by AUC) is similar between extended-release tablets and immediate-release tablets.

Absorption

Saxagliptin

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. Saxagliptin may be administered with or without food. Food has no significant effect on the pharmacokinetics of saxagliptin when administered as KOMBIGLYZE XR combination tablets.

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Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release. Food has no significant effect on the pharmacokinetics of metformin when administered as KOMBIGLYZE XR combination tablets.

Distribution

Saxagliptin

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Metabolism

Saxagliptin

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7.1)*.]

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Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Saxagliptin

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of saxagliptin 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

KOMBIGLYZE XR

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Use of metformin in patients with renal impairment increases the risk for lactic acidosis. Because KOMBIGLYZE XR contains metformin,

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KOMBIGLYZE XR is contraindicated in patients with renal impairment [see *Contraindications (4)* and *Warnings and Precautions (5.3)*].

Hepatic Impairment

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because KOMBIGLYZE XR contains metformin, KOMBIGLYZE XR is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.4)*].

Body Mass Index

Saxagliptin

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

Saxagliptin

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Geriatric

Saxagliptin

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years of age) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively,

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for saxagliptin than young subjects (18-40 years of age). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

KOMBIGLYZE XR should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is normal [see *Warnings and Precautions (5.1, 5.3)*].

Race and Ethnicity

Saxagliptin

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

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Drug Interaction Studies

Specific pharmacokinetic drug interaction studies with KOMBIGLYZE XR have not been performed, although such studies have been conducted with the individual saxagliptin and metformin components.

In Vitro Assessment of Drug Interactions

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate, but is not a significant inhibitor or inducer of P-gp.

In Vivo Assessment of Drug Interactions

Table 3: Effect of Coadministered Drug on Saxagliptin and 5-hydroxy Saxagliptin Systemic Exposures

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC[†]	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Pioglitazone[‡]	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin 5-hydroxy saxagliptin	2.09 0.66	1.63 0.57
Rifampin[§]	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND

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Table 3: Effect of Coadministered Drug on Saxagliptin and 5-hydroxy Saxagliptin Systemic Exposures

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
Limit KOMBIGLYZE XR dose to 2.5 mg/1000 mg once daily when coadministered with strong CYP3A4/5 inhibitors *[see Drug Interactions (7.1) and Dosage and Administration (2.2)]*:					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* Single dose unless otherwise noted

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses

‡ Results exclude one subject

§ The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin.

ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

Table 4: Effect of Saxagliptin on Coadministered Drug Systemic Exposures

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	1.06	1.09
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol and Norgestimate	ethinyl estradiol 0.035 mg and norgestimate 0.250 mg for 21 days	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	1.07 1.10 1.13	0.98 1.09 1.17

* Single dose unless otherwise noted

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† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses
‡ Results include all subjects
ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

Table 5: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution. [See *Warnings and Precautions (5.10)* and *Drug Interactions (7.2).*]					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means

Table 6: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Glyburide	5 mg	850 mg	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	1.02
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF) unless otherwise noted

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‡ Ratio of arithmetic means, p-value of difference <0.05
§ AUC(0-24 hr) reported
¶ Ratio of arithmetic means

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

KOMBIGLYZE XR

No animal studies have been conducted with KOMBIGLYZE XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with saxagliptin and metformin individually.

Saxagliptin

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

Saxagliptin

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

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Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

Saxagliptin

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

12.2 Animal Toxicology and/or Pharmacology

Saxagliptin

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1-3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

13 CLINICAL STUDIES

There have been no clinical efficacy or safety studies conducted with KOMBIGLYZE XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of KOMBIGLYZE XR with coadministered saxagliptin and metformin hydrochloride extended-release tablets has been demonstrated; however, relative bioavailability studies between

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KOMBIGLYZE XR and coadministered saxagliptin and metformin hydrochloride immediate-release tablets have not been conducted. The metformin hydrochloride extended-release tablets and metformin hydrochloride immediate-release tablets have a similar extent of absorption (as measured by AUC) while peak plasma levels of extended-release tablets are approximately 20% lower than those of immediate-release tablets at the same dose.

The coadministration of saxagliptin and metformin immediate-release tablets has been studied in adults with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. In these two trials, treatment with saxagliptin dosed in the morning plus metformin immediate-release tablets at all doses produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

In these two trials, decrease in body weight in the treatment groups given saxagliptin in combination with metformin immediate-release was similar to that in the groups given metformin immediate-release alone. Saxagliptin plus metformin immediate-release was not associated with significant changes from baseline in fasting serum lipids compared to metformin alone.

The coadministration of saxagliptin and metformin immediate-release tablets has also been evaluated in an active-controlled trial comparing add-on therapy with saxagliptin to glipizide in 858 patients inadequately controlled on metformin alone, and in a placebo-controlled trial where a subgroup of 314 patients inadequately controlled on insulin plus metformin received add-on therapy with saxagliptin or placebo, and a trial comparing saxagliptin to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea.

In a 24-week, double-blind, randomized trial, patients treated with metformin immediate-release 500 mg twice daily for at least 8 weeks were randomized to continued treatment with metformin immediate-release 500 mg twice daily or to metformin extended-release either 1000 mg once daily or 1500 mg once daily. The mean change in A1C from baseline to Week 24 was 0.1% (95% confidence interval 0%, 0.3%) for the metformin immediate-release treatment arm, 0.3% (95% confidence interval 0.1%, 0.4%) for the 1000 mg metformin extended-release treatment arm, and 0.1% (95% confidence interval 0%, 0.3%) for the 1500 mg metformin extended-release treatment arm. Results of this trial suggest that patients receiving metformin immediate-release treatment may be safely switched to metformin extended-release once daily at the same total daily dose, up to 2000 mg once daily. Following a switch from metformin immediate-release to

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metformin extended-release, glycemic control should be closely monitored and dosage adjustments made accordingly.

Saxagliptin Morning and Evening Dosing

A 24-week monotherapy trial was conducted to assess a range of dosing regimens for saxagliptin. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of saxagliptin, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or saxagliptin; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either saxagliptin 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of −0.4% and −0.3%, respectively).

13.1 Coadministration of Saxagliptin with Metformin Immediate-Release in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, active-controlled trial to evaluate the efficacy and safety of saxagliptin coadministered with metformin immediate-release in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: saxagliptin 5 mg + metformin immediate-release 500 mg, saxagliptin 10 mg + metformin immediate-release 500 mg, saxagliptin 10 mg + placebo, or metformin immediate-release 500 mg + placebo (the maximum recommended approved saxagliptin dose is 5 mg daily; the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose and the 10 mg dosage is not an approved dosage). Saxagliptin was dosed once daily. In the 3 treatment groups using metformin immediate-release, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during this study were treated with pioglitazone rescue as add-on therapy.

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Coadministration of saxagliptin 5 mg plus metformin immediate-release provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin immediate-release (Table 7).

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin Coadministration with Metformin Immediate-Release in Treatment-Naive Patients*

Efficacy Parameter	Saxagliptin 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−41§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

13.2 Addition of Saxagliptin to Metformin Immediate-Release

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with metformin immediate-release in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

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Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin immediate-release at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of saxagliptin or placebo in addition to their current dose of open-label metformin immediate-release (the maximum recommended approved saxagliptin dose is 5 mg daily; the 10 mg daily dose of saxagliptin does not provide greater efficacy than the 5 mg daily dose and the 10 mg dosage is not an approved dosage). Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of saxagliptin and metformin immediate-release were not permitted.

Saxagliptin 2.5 mg and 5 mg add-on to metformin immediate-release provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin immediate-release (Table 8). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the saxagliptin 2.5 mg add-on to metformin immediate-release group, 13% in the saxagliptin 5 mg add-on to metformin immediate-release group, and 27% in the placebo add-on to metformin immediate-release group.

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Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of Saxagliptin as Add-On Combination Therapy with Metformin Immediate-Release*

Efficacy Parameter	Saxagliptin 2.5 mg + Metformin N=192	Saxagliptin 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

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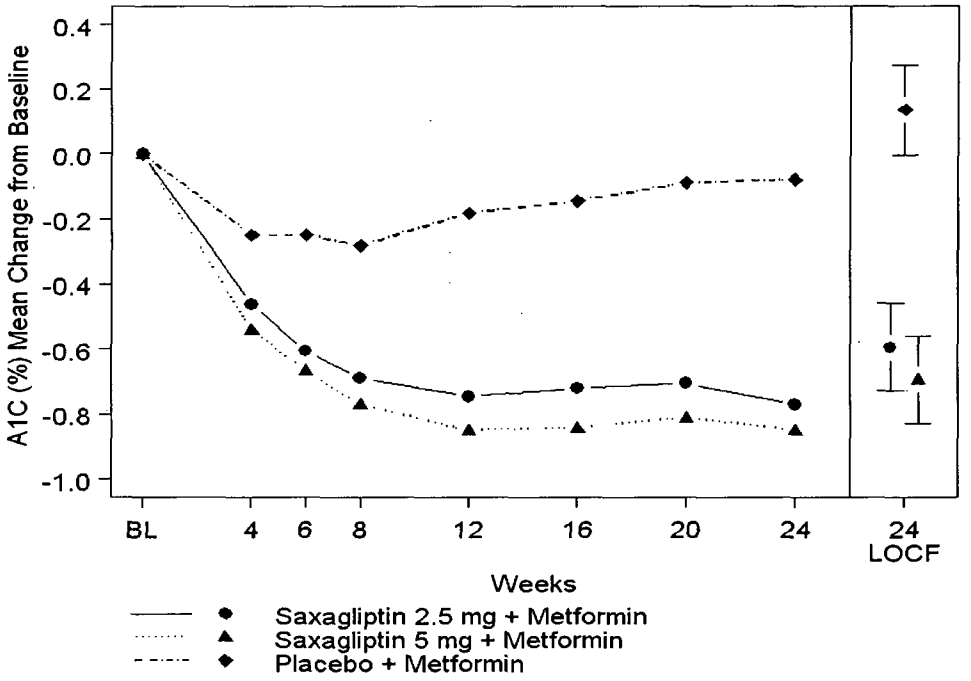
Figure 1: **Mean Change from Baseline in A1C in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin Immediate-Release***



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

13.3 Saxagliptin Add-On Combination Therapy with Metformin Immediate-Release versus Glipizide Add-On Combination Therapy with Metformin Immediate-Release

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin immediate-release alone were randomized to double-blind add-on therapy with saxagliptin or glipizide. Patients were required to be on a stable dose of metformin immediate-release (at least 1500 mg daily) for at least 8 weeks prior to enrollment.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin immediate-release (1500-3000 mg based on their prestudy dose). Following the lead-in period, eligible patients were randomized to 5 mg of saxagliptin or 5 mg of glipizide in addition to their current dose of open-label metformin immediate-release. Patients in the glipizide plus metformin immediate-release

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group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, saxagliptin and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin immediate-release therapy (Table 9). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with saxagliptin compared to a mean weight gain of 1.1 kg in patients treated with glipizide (p<0.0001).

Table 9: Glycemic Parameters at Week 52 in an Active-Controlled Trial of Saxagliptin versus Glipizide in Combination with Metformin Immediate-Release*

Efficacy Parameter	Saxagliptin 5 mg + Metformin N=428	Titrated Glipizide + Metformin N=430
Hemoglobin A1C (%)	**N=423**	**N=423**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean†)	−0.6	−0.7
Difference from glipizide + metformin (adjusted mean†)	0.1	
95% Confidence Interval	(−0.02, 0.2)‡	
Fasting Plasma Glucose (mg/dL)	**N=420**	**N=420**
Baseline (mean)	162	161
Change from baseline (adjusted mean†)	−9	−16
Difference from glipizide + metformin (adjusted mean†)	6	
95% Confidence Interval	(2, 11)§	

* Intent-to-treat population using last observation on study.

† Least squares mean adjusted for baseline value.

‡ Saxagliptin + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%.

§ Significance not tested.

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13.4 Saxagliptin Add-On Combination Therapy with Insulin (with or without Metformin Immediate-Release)

A total of 455 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin immediate-release (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin immediate-release if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either saxagliptin 5 mg or placebo. Doses of the antidiabetic therapies were to remain stable but patients were rescued and allowed to adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with saxagliptin 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 10). Similar mean reductions in A1C versus placebo were observed for patients using saxagliptin 5 mg add-on to insulin alone and saxagliptin 5 mg add-on to insulin in combination with metformin immediate-release (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the saxagliptin group and 32% in the placebo group.

The mean daily insulin dose at baseline was 53 units in patients treated with saxagliptin 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the saxagliptin 5 mg group and 5 units for the placebo group.

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Table 10: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Insulin*

Efficacy Parameter	Saxagliptin 5 mg + Insulin (+/– Metformin) N=304	Placebo + Insulin (+/– Metformin) N=151
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean†)	−0.7	−0.3
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	**N=262**	**N=129**
Baseline (mean)	251	255
Change from baseline (adjusted mean†)	−27	−4
Difference from placebo (adjusted mean†)	−23§	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value and metformin use at baseline.

‡ p-value <0.0001 compared to placebo + insulin

§ p-value <0.05 compared to placebo + insulin

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 17% (52/300) with saxagliptin in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

13.5 Saxagliptin Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin in combination with metformin plus a sulfonylurea in patients with inadequate glycemic control (A1C ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow

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assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind saxagliptin (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

Saxagliptin in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 11). The percentage of patients who discontinued for lack of glycemic control was 6% in the saxagliptin group and 5% in the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of Saxagliptin as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	Saxagliptin 5 mg + Metformin plus Sulfonylurea N=129	Placebo + Metformin plus Sulfonylurea N=128
Hemoglobin A1C (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.1
Difference from placebo (adjusted mean†)	−0.7‡	
95% Confidence Interval	(−0.9, −0.5)	
2-hour Postprandial Glucose (mg/dL)	**N=115**	**N=113**
Baseline (mean)	268	262
Change from baseline (adjusted mean†)	−12	5
Difference from placebo (adjusted mean†)	−17§	
95% Confidence Interval	(−32, −2)	

* Intent-to-treat population using last observation prior to discontinuation.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin plus sulfonylurea

§ p-value <0.05 compared to placebo + metformin plus sulfonylurea

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with saxagliptin in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

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14 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KOMBIGLYZE™ XR (saxagliptin and metformin HCl extended-release) tablets have markings on both sides and are available in the strengths listed in Table 12.

Table 12: KOMBIGLYZE XR Tablet Presentations

Tablet Strength (saxagliptin and metformin HCl extended-release)	Film-Coated Tablet Color/Shape	Tablet Markings
5 mg/500 mg	light brown to brown, biconvex, capsule-shaped	"5/500" on one side and "4221" on the reverse, in blue ink
5 mg/1000 mg	pink, biconvex, capsule-shaped	"5/1000" on one side and "4223" on the reverse, in blue ink
2.5 mg/1000 mg	pale yellow to light yellow, biconvex, capsule-shaped	"2.5/1000" on one side and "4222" on the reverse, in blue ink

Pack Size

Please refer to the outer carton for pack size.

Storage and Handling

Store below 30°C.

Shelf-life

Please refer to expiry date on the outer carton.

ONGLYZA and Kombiglyze are trademarks of Bristol-Myers Squibb Company.

Manufactured by:
Bristol-Myers Squibb Company
4601 Highway 62 East, Mount Vernon, Indiana 47620, USA

Marketed by:
Bristol-Myers Squibb Taiwan Limited
and
AstraZeneca Taiwan Limited

Revised: June 2013

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ANNEXURE-N

2714

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ESTABLISHED 1827

Remfry & Sagar

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New Delhi National Capital Region
India

Tel: 91-124-280 6100 & 91-124-465 6100 Fax: 91-124-280 6101 & 91-124-257 2123 Video Call: 91-124-465 6115
E-Mail: remfry-sagar@remfry.com http://www.remfry.com

E-50/1047/2014

NRA/spl/nkp/IP: 206543-Statement of Working
February 10, 2014

THE CONTROLLER OF PATENTS
THE PATENT OFFICE
MUMBAI

Dear Sirs,

Re: SUBMISSION OF STATEMENT OF
COMMERCIAL WORKING FOR THE YEAR 2013 FOR
Indian Patent no. 206543 (IN/PCT/2002, 01154/MUM)

We have the honour to submit statement of working on Form 27 giving details of commercial working for the calendar year 2013 in respect of above-mentioned patent.

Yours faithfully,

Neeraj Raina

[NEERAJ RAINA]
Of Remfry & Sagar
Attorney for the Applicant(s)

Enclosures:
Form-27 (in duplicate)

पेटेन्ट कार्यालय

12 FEB 2014

Chennai Office : 376-B (Old No.202) Avvai Shanmugam Salai,Gopalapuram Chennai - 600 086, India
Tel & Fax : 91-44-4263 7392 E-Mail : remfry-sagar@remfry.com

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12 FEB 2014

E-50/1046/2014

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ORIGINAL

FORM 27
THE PATENTS ACT, 1970
(39 OF 1970)
&
THE PATENTS RULES, 2003
STATEMENT REGARDING THE WORKING
OF PATENTED INVENTION ON COMMERCIAL SCALE IN INDIA

(See Section 146(2) and Rule 131(1))

In the matter of Patent No. **206543**, of 2002

We, BRISTOL-MYERS SQUIBB COMPANY, of P.O. Box 4000, Lawrenceville-Princeton Road, Princeton, New Jersey 08543-4000, United States of America,

The patentees of licensees under Patent No. **206543** hereby furnish the following statement regarding the working of the patented invention referred to above on a commercial scale in India for the year 2013:

(i) The patented invention
(√) worked ( ) not worked

(a) If not worked reasons for not working and steps being taken for working of the invention:

(b) If worked: quantum and value (in Rupees), of the patented product:

(i) Manufactured in India: NA
(ii) Imported from other countries. (Give Country wise details):
Ireland (ONGLYZA): Quantum-700,078; value- Rs. 541,778.
USA (KOMBIGLYZE): Quantum- 123,777; value- Rs. 112,851.

(ii) The licenses and sub-licenses granted during the year: None

(iii) State whether public requirement has been met partly/adequately/to the fullest extent at reasonable price: Patentee believes that the public requirement has been met adequately at reasonable price.

The facts and matters stated above are true to the best of our knowledge, information and belief.

Dated February 10, 2014

[NEERAJ RAINA]
OF REMFRY & SAGAR
AGENT FOR THE PATENTEES

TO, THE CONTROLLER OF PATENTS

IPO MUMBAI 29-06-2015 16:01

12 FEB 2014

Analysis of Exports of saxagliptin

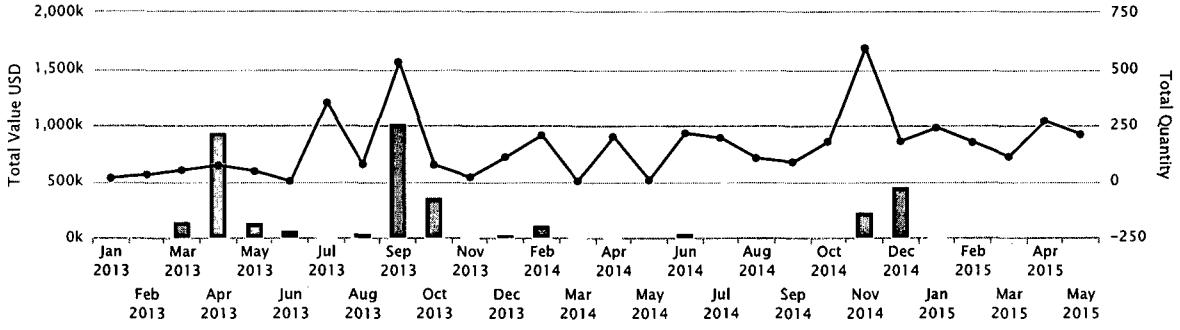
India exported saxagliptin worth USD 3,696,275 with total quantity of 4,354. Canada is the largest buyer of saxagliptin accounting for exports worth USD 2,217,381 followed by Slovenia and United States which imported saxagliptin worth USD 828,386 and USD 502,240 respectively.

Banglore Air Cargo accounted for 60% of exports followed by Hyderabad Air Cargo and Bombay Air Cargo which account for 37.6% and 1.3% of exports respectively.

Average price of saxagliptin per unit is USD 848.90 and average value per shipment is 20,198

Click here to view detailed Export data of saxagliptin

Total Volume & Value of Exports



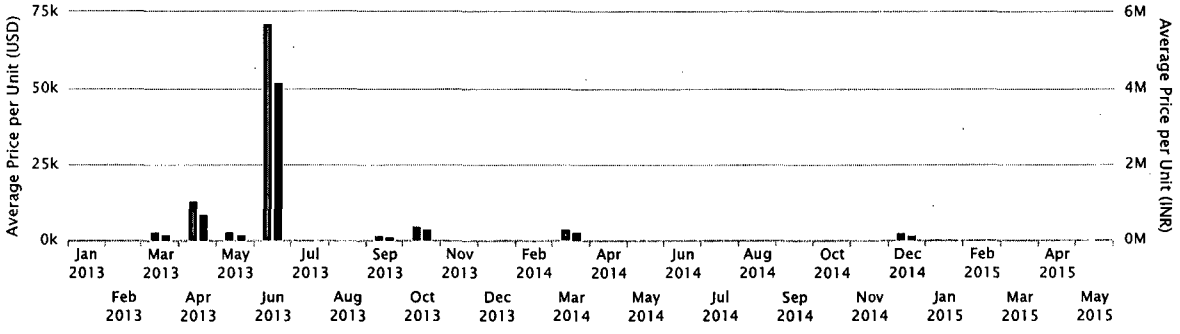
It's gone. Undo

What was wrong with this ad?

Repetitive Inappropriate Irrelevant

Google

Average Price per Unit



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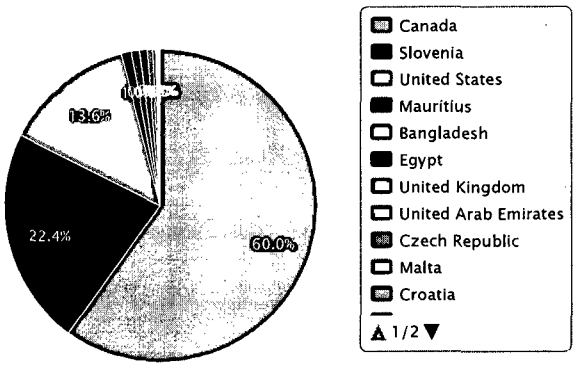
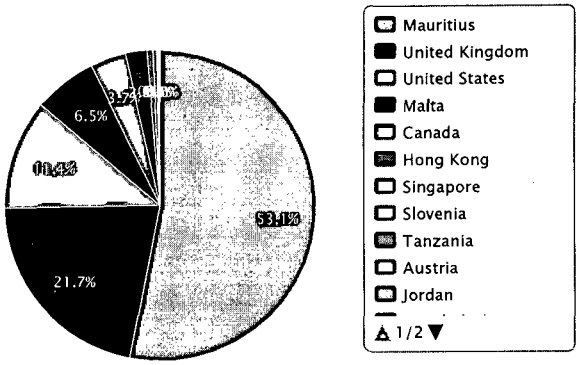
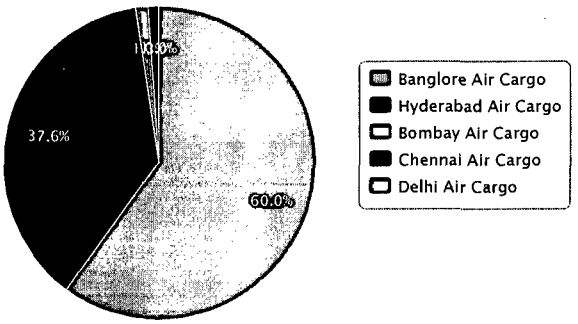
Total Value of Exports by Countries (USD)



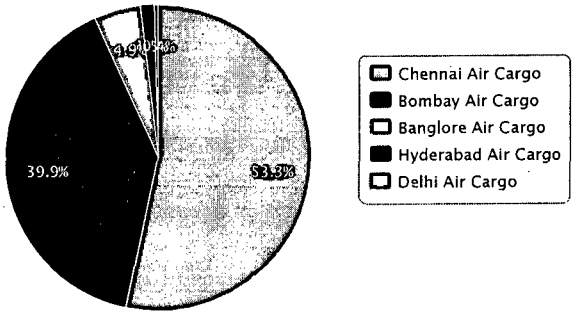
Total Quantity of Exports by Countries



Total Value of Exports by Loading Port (USD)



Total Quantity of Exports by Loading Port (USD)



Filter by

HTS Code

30 (145)

29 (38)

Destination

United Kingdom (90)
Mauritius (27)
Slovenia (12)
United States (11)
Canada (10)
Malta (8)
Hong Kong (6)
Singapore (4)
Egypt (3)
Austria (2)

Port of Loading

Bombay Air Cargo (113)
Chennai Air Cargo (32)
Hyderabad Air Cargo (23)
Banglore Air Cargo (10)
Delhi Air Cargo (5)

Month

Jan 2013 (1)
Feb 2013 (1)
Mar 2013 (2)
Apr 2013 (5)
May 2013 (3)
Jun 2013 (1)
Jul 2013 (2)
Aug 2013 (4)
Sep 2013 (5)
Oct 2013 (3)
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Apr 2014 (3)
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Jun 2014 (18)
Jul 2014 (5)
Aug 2014 (15)
Sep 2014 (10)
Oct 2014 (12)
Nov 2014 (16)
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Jan 2015 (12)
Feb 2015 (9)
Mar 2015 (6)
Apr 2015 (12)

Unit Quantity

PAC (133)
KGS (32)
NOS (14)
BOX (3)
LOT (1)

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Detailed Export Data of saxagliptin

183 export shipment records found.
Click here to view detailed analysis and trends of Export of saxagliptin

Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
20-May-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	7	5,481	783
18-May-2015	30045090	ONGLYZA 2.5MG [SAXAGLIPTIN], MANUFACTURER :BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-	United Kingdom	Bombay Air Cargo	PAC	12	8,986	749
12-May-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] ,MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,672	779
11-May-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,598	766
7-May-2015	30049039	KOMBIGLYZE XR TAB (SAXAGLIPTIN/METFOR 5/500 MG)	Mauritius	Chennai Air Cargo	PAC	98	112,284	1,146
7-May-2015	30049039	KOMBIGLYZE XR TAB (SAXAGLIPTIN/METFOR 5/1000 MG)	Mauritius	Chennai Air Cargo	PAC	50	57,288	1,146
6-May-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	19	14,595	768
6-May-2015	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	12	8,854	738
30-Apr-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	21	16,184	771
30-Apr-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	19	14,654	771
30-Apr-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	150	144,389	963
28-Apr-2015	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG2 8TAB	Malta	Banglore Air Cargo	PAC	20	20,430	1,021
27-Apr-2015	30045090	ONGLYZA 5MG (SAXAGLIPTIN),MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915, MFD.DATE:MAY-14, EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,624	771
21-Apr-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN], MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4J81915, MFD.DATE:MAY-14,EXP.DATE :APR-17	United Kingdom	Bombay Air Cargo	PAC	20	15,636	782
21-Apr-2015	30045090	ONGLYZA 2.5MG [SAXAGLIPTIN], MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4A83886, MFD.DATE:AUG-13,EXP.DATE :AUG	United Kingdom	Bombay Air Cargo	PAC	6	4,505	751
21-Apr-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN], MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4J81914, MFD.DATE:APR-14,EXP.DATE :MAR-	United Kingdom	Bombay Air Cargo	PAC	6	4,691	782
18-Apr-2015	30049099	ONGLYZA 2.5MG (SAXAGLIPTIN) SIZE-28 TABS/PACK (PHARMACEUTICALS MEDICINES)	United Kingdom	Delhi Air Cargo	NOS	3	3,029	1,010
18-Apr-2015	30049099	ONGLYZA 2.5MG (SAXAGLIPTIN) SIZE-28 TABS/PACK (PHARMACEUTICALS MEDICINES)	United Kingdom	Delhi Air Cargo	NOS	6	6,033	1,005
16-Apr-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN],MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4J81914, MFD.DATE:APR-14, EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	7	5,503	786
16-Apr-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] ,MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:4J81915, MFD.DATE:MAY-14, EXP.DATE:APR-1	United Kingdom	Bombay Air Cargo	PAC	7	5,503	786
30-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,698	783
30-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,672	779
21-Mar-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5MG)	Mauritius	Chennai Air Cargo	PAC	50	47,821	956
19-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,631	772
19-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	31	24,235	782
2-Mar-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER- BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.- 4J81914 MFD.DATE-APR-14 EXP.DATE-MA	United Kingdom	Bombay Air Cargo	PAC	12	9,374	781

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23-Feb-2015	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,505	751
23-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	34	26,580	782
9-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	19	14,815	780
9-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	27	21,154	783

<< 1 2 3 4 5 6 7 >>

Filter by

HTS Code
- 30 (145)
- 29 (38)

Destination
- United Kingdom (90)
- Mauritius (27)
- Slovenia (12)
- United States (11)
- Canada (10)
- Malta (8)
- Hong Kong (6)
- Singapore (4)
- Egypt (3)
- Austria (2)

Port of Loading
- Bombay Air Cargo (113)
- Chennai Air Cargo (32)
- Hyderabad Air Cargo (23)
- Banglore Air Cargo (10)
- Delhi Air Cargo (5)

Month
- Jun 2014 (18)
- Nov 2014 (16)
- Aug 2014 (15)
- Dec 2014 (13)
- Oct 2014 (12)
- Jan 2015 (12)
- Apr 2015 (12)
- Sep 2014 (10)
- Feb 2015 (9)
- May 2015 (8)

Unit Quantity
- PAC (133)
- KGS (32)
- NOS (14)
- BOX (3)
- LOT (1)

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harmless medicines 12 2011 100 eou 2011 valid valid upto free samples pantoprazole sodium pharmaceutical products amino acids organic chemical research use chemical not not covered bulk drug

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Detailed Export Data of saxagliptin

183 export shipment records found.
Click here to view detailed analysis and trends of Export of saxagliptin

Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
30-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81915,MFD.DATE:MAY-14,EXP.DATE:APR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,698	783
30-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,672	779
21-Mar-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5MG)	Mauritius	Chennai Air Cargo	PAC	50	47,821	956
19-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	6	4,631	772
19-Mar-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	31	24,235	782
2-Mar-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER- BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.- 4J81914 MFD.DATE- APR-14 EXP.DATE-MA	United Kingdom	Bombay Air Cargo	PAC	12	9,374	781
23-Feb-2015	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,505	751
23-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	34	26,580	782
9-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	19	14,815	780
9-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4J81914,MFD.DATE:APR-14,EXP.DATE:MAR-17	United Kingdom	Bombay Air Cargo	PAC	27	21,154	783
6-Feb-2015	30049039	KOMBIGLYZE XR (SAXAGLIPTIN/METFORMIN 5/1000 MG)	Mauritius	Chennai Air Cargo	PAC	50	56,024	1,120
2-Feb-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER : BRISTOL MYERS SQUIBB, S.R.L. BATCHNO. 4J81914 MFD.DATE. APR-14 EXP.DATE. M	United Kingdom	Bombay Air Cargo	PAC	7	5,497	785
2-Feb-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L. BATCH NO. 4E79149 MFD.DATE. DEC-13 EXP.DATE.DEC-	United Kingdom	Bombay Air Cargo	PAC	12	9,048	754
2-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79525,MFD.DATE:JAN-14,EXP.DATE:JAN-17	United Kingdom	Bombay Air Cargo	PAC	6	4,517	753
2-Feb-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79149,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	14	10,539	753
30-Jan-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	50	46,724	934
28-Jan-2015	29339900	5-HYDROXY SAXAGLIPTIN HYDROCHLORIDEWORKING STANDARD(25 MG= 1 PACK)	Croatia	Bombay Air Cargo	PAC	1	183,900	183,900
19-Jan-2015	30045090	ONGLYZA 5MG(SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79146,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	12	8,974	748
19-Jan-2015	30045090	ONGLYZA 5MG (SAXAGLIPTIN),MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79146,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,465	744
12-Jan-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	13	9,691	745
12-Jan-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79146,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	18	13,418	745
8-Jan-2015	29339900	SAXAGLIPTIN HYDROCHLORIDE RSSS IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	72,258	36,129,000,000
5-Jan-2015	29339900	SAXAGLIPTIN HYDROCHLORIDE	United Arab Emirates	Hyderabad Air Cargo	KGS	0	493,839	4,938,390
3-Jan-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,469	745
3-Jan-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER : BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.: 4D80642 MFD.DATE.: DEC-13 EXP.DATE:D	United Kingdom	Bombay Air Cargo	PAC	14	10,445	746
2-Jan-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	100	94,170	942

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2-Jan-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	20	18,834	942
20-Dec-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D8064Z,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	13	9,610	739
18-Dec-2014	29321990	SAXAGLIPTIN AMIDE IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000
18-Dec-2014	29321990	SAXAGLIPTIN CYCLIC AMIDE IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000

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Destination

United Kingdom (90)
Mauritius (27)
Slovenia (12)
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Port of Loading

Bombay Air Cargo (113)
Chennai Air Cargo (32)
Hyderabad Air Cargo (23)
Banglore Air Cargo (10)
Delhi Air Cargo (5)

Month

Jun 2014 (18)
Nov 2014 (16)
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Dec 2014 (13)
Oct 2014 (12)
Jan 2015 (12)
Apr 2015 (12)
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Detailed Export Data of saxagliptin

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Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
12-Jan-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4E79146,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	18	13,418	745
8-Jan-2015	29339900	SAXAGLIPTIN HYDROCHLORIDE RSSS IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	72,258	36,129,000,000
5-Jan-2015	29339900	SAXAGLIPTIN HYDROCHLORIDE	United Arab Emirates	Hyderabad Air Cargo	KGS	0	493,839	4,938,390
3-Jan-2015	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,469	745
3-Jan-2015	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER : BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.: 4D80642 MFD.DATE.: DEC-13 EXP.DATE:D	United Kingdom	Bombay Air Cargo	PAC	14	10,445	746
2-Jan-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	100	94,170	942
2-Jan-2015	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	20	18,834	942
20-Dec-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	13	9,610	739
18-Dec-2014	29321990	SAXAGLIPTIN AMIDE IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000

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18-Dec-2014	29321990	SAXAGLIPTIN CYCLIC AMIDE IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000
18-Dec-2014	29321990	SAXAGLIPTIN KETO IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000
18-Dec-2014	29321990	SAXAGLIPTIN BOC PROTECTED IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000
18-Dec-2014	29321990	SAXAGLIPTIN DESHYDROXY IMPURITY	Slovenia	Hyderabad Air Cargo	KGS	0	79,436	3,971,793,000
15-Dec-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
8-Dec-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	12	9,004	750
8-Dec-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,502	750
6-Dec-2014	29339900	SAXAGLIPTIN HYDROCHLORIDE	Slovenia	Hyderabad Air Cargo	KGS	10	27,602,096	2,760,210
1-Dec-2014	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER : BRISTOL MYERS SQUIBB, S.R.L.BATCH NO:4D80642MFD.DATE:DEC-13 EXP.DATE: DEC-1	United Kingdom	Bombay Air Cargo	PAC	13	9,754	750
1-Dec-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	100	93,682	937
1-Dec-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	20	18,736	937
29-Nov-2014	30045090	ONGLYZA 2.5MG(SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	24	18,036	752
29-Nov-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	18	13,527	752
29-Nov-2014	30049099	ONGLYZA 2.5MG (SAXAGLIPTIN) SIZE -28 TABS/PACK (PHARMACEUTICALS MEDICINES)	United Kingdom	Delhi Air Cargo	NOS	3	2,857	952
27-Nov-2014	29332990	SAXAGLIPTIN HYDROCHLORIDE	Slovenia	Hyderabad Air Cargo	KGS	5	13,821,084	2,764,217
17-Nov-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG 28TAB	Malta	Banglore Air Cargo	PAC	35	33,443	956

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15-Nov-2014	30049099	SAXAGLIPTIN TABLETS 2.5MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN TABLETS 5MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 5MG/500MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 5MG/1000MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 2.5MG/1000MG	United States	Bombay Air Cargo	NOS	90	608	7

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HTS Code
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Destination
United Kingdom (90)
Mauritius (27)
Slovenia (12)
United States (11)
Canada (10)
Malta (8)
Hong Kong (6)
Singapore (4)
Egypt (3)
Austria (2)

Port of Loading
Bombay Air Cargo (113)
Chennai Air Cargo (32)
Hyderabad Air Cargo (23)
Banglore Air Cargo (10)
Delhi Air Cargo (5)

Month
Jun 2014 (18)
Nov 2014 (16)
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Dec 2014 (13)
Oct 2014 (12)
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Detailed Export Data of saxagliptin

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Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
29-Nov-2014	30045090	ONGLYZA 2.5MG(SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	24	18,036	752
29-Nov-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	18	13,527	752
29-Nov-2014	30049099	ONGLYZA 2.5MG (SAXAGLIPTIN) SIZE -28 TABS/PACK (PHARMACEUTICALS MEDICINES)	United Kingdom	Delhi Air Cargo	NOS	3	2,857	952
27-Nov-2014	29332990	SAXAGLIPTIN HYDROCHLORIDE	Slovenia	Hyderabad Air Cargo	KGS	5	13,821,084	2,764,217
17-Nov-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG 28TAB	Malta	Banglore Air Cargo	PAC	35	33,443	956
15-Nov-2014	30049099	SAXAGLIPTIN TABLETS 2.5MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN TABLETS 5MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 5MG/500MG	United States	Bombay Air Cargo	NOS	90	608	7
15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 5MG/1000MG	United States	Bombay Air Cargo	NOS	90	608	7

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15-Nov-2014	30049099	SAXAGLIPTIN AND EXTENDED RELEASE METFORMIN HYDROCHLORIDE TABLETS 2.5MG/1000MG	United States	Bombay Air Cargo	NOS	90	608	7
11-Nov-2014	29339900	SAXAGLIPTIN HYDROCLORIDE BM14002749	Saudi Arabia	Banglore Air Cargo	KGS	0	152	30,450
11-Nov-2014	29339900	SAXAGLIPTIN HYDROCLORIDE BM14002749	Saudi Arabia	Banglore Air Cargo	KGS	0	30	304,500
8-Nov-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	32	24,029	751
3-Nov-2014	29141990	SAXAGLIPTIN HCL REFERENCE STANDARD	United Kingdom	Hyderabad Air Cargo	KGS	0	485,913	4,859,125,000
1-Nov-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	13	9,754	750
1-Nov-2014	30045090	ONGLYZA 5MG [SAXAGLIPTIN],MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	14	10,504	750
18-Oct-2014	30045090	ONGLYZA 5MG (SAXAGLIPTIN),MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	19	14,325	754
17-Oct-2014	30049039	ONGLYZA TAB (SAXAGLIPTINE 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	40	38,110	953
16-Oct-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,520	753
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	13	9,794	753
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,557	760
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,557	760
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,509	752
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	7	5,261	752
14-Oct-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,524	754
14-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,524	754

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14-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	13	9,802	754
13-Oct-2014	30049039	ONGLYZA TAB (SAXAGLIPTINE 5MG)	Mauritius	Chennai Air Cargo	PAC	50	47,648	953
20-Sep-2014	30049099	ONGLYZA TABLETS (10 PACKx28=280 TABS)EACH TABS CONT: SAXAGLIPTIN 2.5MG	Hong Kong	Bombay Air Cargo	PAC	10	13,195	1,320
20-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	20	14,868	743

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HTS Code

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Destination

United Kingdom (90)
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Austria (2)

Port of Loading

Bombay Air Cargo (113)
Chennai Air Cargo (32)
Hyderabad Air Cargo (23)
Banglore Air Cargo (10)
Delhi Air Cargo (5)

Month

Jun 2014 (18)
Nov 2014 (16)
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Unit Quantity

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Detailed Export Data of saxagliptin

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Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,557	760
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,557	760
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,509	752
16-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	7	5,261	752
14-Oct-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,524	754
14-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4D80642,MFD.DATE:DEC-13,EXP.DATE:DEC-16	United Kingdom	Bombay Air Cargo	PAC	6	4,524	754
14-Oct-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	13	9,802	754
13-Oct-2014	30049039	ONGLYZA TAB (SAXAGLIPTINE 5MG)	Mauritius	Chennai Air Cargo	PAC	50	47,648	953
20-Sep-2014	30049099	ONGLYZA TABLETS (10 PACKx28=280 TABS)EACH TABS CONT: SAXAGLIPTIN 2.5MG	Hong Kong	Bombay Air Cargo	PAC	10	13,195	1,320

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Google

20-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	20	14,868	743
20-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	12	8,899	742
19-Sep-2014	29339900	SAXAGLIPTIN HYDROCHLORIDE	United Arab Emirates	Hyderabad Air Cargo	KGS	0	267,799	2,677,990
15-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	12	8,978	748
12-Sep-2014	30044090	TAB.ONGLYZA 2.5 MG(SAXAGLIPTIN)	Tanzania	Bombay Air Cargo	PAC	2	1,884	942
8-Sep-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,493	749
8-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,493	749
8-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C86774,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	7	5,242	749
8-Sep-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C85110,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	12	8,986	749
30-Aug-2014	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C85110,MFD.DATE: NOV-13,EXP.DATE: NOV-1	United Kingdom	Bombay Air Cargo	PAC	13	9,783	753
30-Aug-2014	30045090	ONGLYZA 5MG [SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C86774,MFD.DATE: NOV-13,EXP.DATE: NOV-1	United Kingdom	Bombay Air Cargo	PAC	19	14,298	753
26-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	9	6,822	758
26-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C86774,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	10	7,579	758
25-Aug-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,504	751
23-Aug-2014	30049099	Saxagliptin FC Tablets - 2.5 MG,FD212-19B (1 NOS 550 TABLETS)	Canada	Chennai Air Cargo	NOS	1	82	82
23-Aug-2014	30049099	Saxagliptin FC Tablets - 5 MG,FD212-20B(1 NOS 550 TABLETS)	Canada	Chennai Air Cargo	NOS	1	109	109
16-Aug-2014	30049099	SAXAGLIPTIN TABLETS 2.5 MG(1 NOS 2598 TABLETS)	Canada	Chennai Air Cargo	NOS	1	222	222

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16-Aug-2014	30049099	SAXAGLIPTIN TABLETS 5 MG(1 NOS 2598 TABLETS)	Canada	Chennai Air Cargo	NOS	1	334	334
14-Aug-2014	30044090	MEDICINES - TAB.KOMBIGLYZE 5 MG/1000 MG(SAXAGLIPTIN)	Tanzania	Bombay Air Cargo	PAC	5	1,510	302
12-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
8-Aug-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3C82486,MFD.DATE:DEC-12,EXP.DATE:DEC-15	United Kingdom	Bombay Air Cargo	PAC	2	1,476	738

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Destination
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Port of Loading
Bombay Air Cargo (113)
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Detailed Export Data of saxagliptin

183 export shipment records found.
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Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
26-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	9	6,822	758
26-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C86774,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	10	7,579	758
25-Aug-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,504	751
23-Aug-2014	30049099	Saxagliptin FC Tablets - 2.5 MG,FD212-19B (1 NOS 550 TABLETS)	Canada	Chennai Air Cargo	NOS	1	82	82
23-Aug-2014	30049099	Saxagliptin FC Tablets - 5 MG,FD212-20B(1 NOS 550 TABLETS)	Canada	Chennai Air Cargo	NOS	1	109	109
16-Aug-2014	30049099	SAXAGLIPTIN TABLETS 2.5 MG(1 NOS 2598 TABLETS)	Canada	Chennai Air Cargo	NOS	1	222	222
16-Aug-2014	30049099	SAXAGLIPTIN TABLETS 5 MG(1 NOS 2598 TABLETS)	Canada	Chennai Air Cargo	NOS	1	334	334
14-Aug-2014	30044090	MEDICINES - TAB.KOMBIGLYZE 5 MG/1000 MG(SAXAGLIPTIN)	Tanzania	Bombay Air Cargo	PAC	5	1,510	302
12-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750

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8-Aug-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3CB2486,MFD.DATE:DEC-12,EXP.DATE:DEC-15	United Kingdom	Bombay Air Cargo	PAC	2	1,476	738
8-Aug-2014	30045090	ONGLYZA 2.5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4A83886,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	4	2,952	738
8-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN]MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	7	5,165	738
2-Aug-2014	30045090	ONGLYZA 5MG[SAXAGLIPTIN] MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:4C87653,MFD.DATE:NOV-13,EXP.DATE:NOV-16	United Kingdom	Bombay Air Cargo	PAC	20	15,009	750
26-Jul-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	13	9,725	748
23-Jul-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG (PACK OF 28TAB)	Malta	Bombay Air Cargo	PAC	35	35,856	1,024
7-Jul-2014	30049039	ONGLYZA 5 MG TAB (SAXAGLIPTINE 5 MG)	Mauritius	Chennai Air Cargo	PAC	120	114,975	958
1-Jul-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG (PACK OF 28TAB)	Malta	Bombay Air Cargo	PAC	20	20,427	1,021
1-Jul-2014	30045090	ONGLYZA5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L. ,BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,484	747
30-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,477	746
30-Jun-2014	29225090	SAXAGLIPTIN MONOHYDRATE FOR US REGULATORY	Slovenia	Hyderabad Air Cargo	KGS	0	887,730	4,438,650
30-Jun-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5MG)	Mauritius	Chennai Air Cargo	PAC	40	38,454	961
28-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3M54802,MFD.DATE.:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	14	11,511	822
21-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,438	740
20-Jun-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG (PACK OF 28TAB)	Malta	Bombay Air Cargo	PAC	47	48,238	1,026
19-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13 ,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,883	814
18-Jun-2014	29339900	SAXAGLIPTIN MONOHYDRATE BULK DRUG	Egypt	Bombay Air Cargo	KGS	0	498,987	2,494,935

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13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN)MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.: 3M54802, MFD.DATE: AUG-13, EXP.DATE:	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
13-Jun-2014	30045090	ONGLYZA 2.5MG(SAXAGLIPTIN)MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L., BATCHNO.: 3C82486, MFD.DATE: DEC-12, EXP.DATE	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3K75732, MFD.DATE:JUN-13, EXP.DATE:JUN-16	United Kingdom	Bombay Air Cargo	PAC	1	814	814
13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3M54802, MFD.DATE:AUG-13, EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	19	15,464	814

<< 1 2 3 4 5 6 7 >>

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Destination
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Port of Loading
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- Banglore Air Cargo (10)
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Month
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Detailed Export Data of saxagliptin

183 export shipment records found.
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Date	HS Code	Description	Destination	Port of Loading	Unit	Quantity	Value (INR)	Per Unit (INR)
30-Jun-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5MG)	Mauritius	Chennai Air Cargo	PAC	40	38,454	961
28-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3M54802,MFD.DATE.:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	14	11,511	822
21-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,438	740
20-Jun-2014	30043990	ONGLYZA 5 SAXAGLIPTIN 5MG (PACK OF 28TAB)	Malta	Bombay Air Cargo	PAC	47	48,238	1,026
19-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.,BATCH NO.:3M54802,MFD.DATE:AUG-13 ,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,883	814
18-Jun-2014	29339900	SAXAGLIPTIN MONOHYDRATE - BULK DRUG	Egypt	Bombay Air Cargo	KGS	0	498,987	2,494,935
13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN)MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.: 3M54802, MFD.DATE: AUG-13, EXP.DATE:	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
13-Jun-2014	30045090	ONGLYZA 2.5MG(SAXAGLIPTIN)MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L., BATCHNO.: 3C82486, MFD.DATE: DEC-12, EXP.DATE	United Kingdom	Bombay Air Cargo	PAC	6	4,498	750
13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3K75732, MFD.DATE:JUN-13, EXP.DATE:JUN-16	United Kingdom	Bombay Air Cargo	PAC	1	814	814

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13-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L., BATCH NO.:3M54802, MFD.DATE:AUG-13, EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	19	15,464	814
11-Jun-2014	30045090	ONGLYZA 2.5MG (SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.: 3C82483 MFD.DATE: JUL-12 EXP.DATE: JU	United Kingdom	Bombay Air Cargo	PAC	10	7,521	752
11-Jun-2014	30045090	ONGLYZA 2.5MG (SAXAGLIPTIN) MANUFACTURER: BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.: 3C82486 MFD.DATE: DEC-12 EXP.DATE:DEC	United Kingdom	Bombay Air Cargo	PAC	2	1,504	752
11-Jun-2014	30045090	ONGLYZA 5MG (SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.:3M54802 MFD.DATE:AUG-13 EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,513	752
11-Jun-2014	30045090	ONGLYZA 5MG(SAXAGLIPTIN) MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L. BATCH NO.:3M54802 MFD.DATE:AUG-13 EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,513	752
3-Jun-2014	29332990	SAXAGLIPTIN HYDROCHLORIDE	Slovenia	Hyderabad Air Cargo	KGS	0	1,059,877	5,299,386
2-Jun-2014	29339900	SAXAGLIPTIN HCL CYCLIC AMIDINE IMPURITY(MG= PACKS)	United States	Hyderabad Air Cargo	PAC	40	186,372	4,659
31-May-2014	30045090	ONGLYZA 5MG (SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.-BATCH NO.3M54802,MFD.DATE:AUG-13,EXP.DATE:AUG-16	United Kingdom	Bombay Air Cargo	PAC	6	4,904	817
31-May-2014	30045090	ONGLYZA 5MG (SAXAGLIPTIN)MANUFACTURER:BRISTOL MYERS SQUIBB, S.R.L.-BATCH NO.3K75732,MFD.DATE:JUN-13,EXP.DATE:JUN-16	United Kingdom	Bombay Air Cargo	PAC	1	817	817
30-Apr-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	160	153,584	960
30-Apr-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	40	38,396	960
11-Apr-2014	29334900	SAXAGLIPTIN HYDROCHLORIDE RSSS IMP(NET QTY:50 MG)	United States	Hyderabad Air Cargo	KGS	0	236,500	4,730,000,000
29-Mar-2014	29372900	SAXAGLIPTIN HYDROCHLORIDE AMIDE MP(1 LOT = 90 MG)	United States	Hyderabad Air Cargo	LOT	1	435,419	435,419
7-Mar-2014	29420090	SAXAGLIPTIN(1PACK = 50MG)	Jordan	Bombay Air Cargo	PAC	1	30,665	30,665
28-Feb-2014	29339900	SAXAGLIPTIN HYDROCHLORIDE	United States	Hyderabad Air Cargo	KGS	1	6,678,954	5,858,731
26-Feb-2014	30045090	ONGLYZA 5MG TAB (SAXAGLIPTIN) - 28s	Singapore	Bombay Air Cargo	PAC	6	6,251	1,042
10-Feb-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 2.5 MG)	Mauritius	Chennai Air Cargo	PAC	50	48,341	967

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10-Feb-2014	30049039	ONGLYZA TAB (SAXAGLIPTIN 5 MG)	Mauritius	Chennai Air Cargo	PAC	150	145,024	967
7-Feb-2014	29339900	SAXAGLIPTIN HYDROCHLORIDE	Egypt	Hyderabad Air Cargo	KGS	0	532,686	3,043,920
24-Dec-2013	30043990	ONGLYZA 5 MG TABS SAXAGLIPTIN (PACK OF 28 TABS)	Hong Kong	Bombay Air Cargo	PAC	20	23,274	1,164
21-Dec-2013	29141990	SAXAGLIPTIN HYDROCHLORIDE REFERNCE STANDARD	United States	Hyderabad Air Cargo	KGS	0	937,827	46,891,345,000

<< 1 2 3 4 5 6 7 >>

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Destination

United Kingdom (90)
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Slovenia (12)
United States (11)
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Hong Kong (6)
Singapore (4)
Egypt (3)
Austria (2)

Port of Loading

Bombay Air Cargo (113)
Chennai Air Cargo (32)
Hyderabad Air Cargo (23)
Banglore Air Cargo (10)
Delhi Air Cargo (5)

Month

Jun 2014 (18)
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Jan 2015 (12)
Apr 2015 (12)
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ANNEXURE-P

S. No.	Country	Application No.	Title	Status
01	India	2950/CHE/2007	A NOVEL PROCESS FOR THE PREPARATION OF CRYSTALLINE MAGNESIUM SALT OF (S)-OMEPRAZOLE DI HYDRATE	Pending
02	India	2382/CHE/2007	PROCESS FOR THE PREPARATION OF NOVEL SALT OF VORICONAZOLE OXALATE FORM C	Pending
03	India	2451/CHE/2010	NOVEL PROCESS FOR THE PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
04	PCT	PCT/IN2012/000121	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Published
05	U.S.A	13/820,568	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
06	Europe	12716665	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Intention to Grant European Patent
07	China	2012/80009854.5	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
08	India	2450/CHE/2010	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
09	PCT	PCT/IN2012/000120	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Published
10	U.S.A	13/820,565	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
11	Europe	12716664.3	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Withdrawal of Appl.
12	China	2012/80009872.3	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
13	India	1533/CHE/2009	IMPROVED PROCESS FOR THE PREPARATION OF OMEPRAZOLE FORM-A	Pending
14	India	1532/CHE/2009	AN IMPROVED PROCESS FOR PREPARATION OF CRYSTALLINE LANSOPRAZOLE	Pending
15	India	4256/CHE/2012	A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXYCARBONYL-3-HYDROXY]ADAMANTYLGLYCINE	Pending
16	PCT	PCT/IN2012/000865	A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXYCARBONYL-3-HYDROXY]ADAMANTYLGLYCINE	Published

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ANNEXURE-P

17	India	5441/CHE/2012	A PROCESS FOR PREPARATION OF TRANS (1R,2R)-CYCLO HEXANE 1,2–DICARBOXYLIC ACID	Pending
18	PCT	PCT/IN2013/000149	A PROCESS FOR PREPARATION OF TRANS (1R,2R)-CYCLO HEXANE 1,2–DICARBOXYLIC ACID	Published
19	India	5063/CHE/2013	NOVEL OXAZOLIDINONE COMPOUNDS	Pending
20	PCT	PCT/IN2014/000018	NOVEL OXAZOLIDINONE COMPOUNDS	Pending
21	India	2254/CHE/2014	NOVEL OXAZOLIDINONE ANTIBACTERIAL COMPOUND	Pending
22	PCT	PCT/IN2014/000497	NOVEL OXAZOLIDINONE ANTIBACTERIAL COMPOUND	Pending

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ANNEXURE-Q

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सूचना
का अधिकार

TELEGRAM : SCINDRECH
दूरभाष/TEL : 26962819, 26567373
(EPBAX) : 26565694, 26562133
: 26565687, 26562144
: 26562134, 26562122
फैक्स/FAX : 26960629, 26529745
Website : http:/www.dsir.gov.in

सत्यमेव जयते

भारत सरकार
विज्ञान और प्रौद्योगिकी मंत्रालय
वैज्ञानिक और औद्योगिक अनुसंधान विभाग
टेक्नोलॉजी भवन, नया महरौली मार्ग,
नई दिल्ली – 110 016
GOVERNMENT OF INDIA
MINISTRY OF SCIENCE AND TECHNOLOGY
Department of Scientific and Industrial Research
Technology Bhavan, New Mehrauli Road,
New Delhi - 110 016

F. No. TU/IV-RD/2186/2015 **Dated: 17th April, 2015**

To

M/s. Lee Pharma Ltd.
Sy. No. 257 & 258/1, Door No. 11-6/56
C-Block, Opp. IDPL Factory, Moosapet Vill.
Balanagar Post
Hyderabad – 500 037

Subject: **RENEWAL / RECOGNITION OF IN-HOUSE R&D UNIT (S)**

Dear Sirs,

This has the reference to renewal of recognition of your in-house R&D unit(s) and also for recognition of in-house R&D unit(s) by the Department of Scientific and Industrial Research.

2. This is to inform you that it has been decided to accord renewal of recognition to the in-house R&D unit(s) of your firm at **(i) Survey No. 10/G-1, Gaddapotharam (Village), Jinnaram (Mandal), Medak (District), Hyderabad** upto **31.03.2017** and fresh recognition to the in-house R&D unit at **(ii) Plot No. V, Phase II, Visakhapatnam Special Economic Zone (VSEZ), Duvvada, Visakhapatnam** from **26.02.2015 to 31.03.2017** by the Department of Scientific and Industrial Research. Terms and Conditions pertaining to this recognition are given overleaf.

3. Kindly acknowledge the receipt of this letter.

Yours faithfully,

(K.V.S.P. Rao)
Scientist-G

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F.No. TU/IV-RD/2186/2015

TERMS AND CONDITIONS OF RECOGNITION OF IN-HOUSE R&D UNITS

1. On receipt of recoginition letter, the firm shall acknowledge by stating that they abide by the terms & conditions of the recognition.

2. In-house R&D units recognised by DSIR are also deemed to be registered. A separate certificate of registration** is issued along with the recognition letter. The recognition would be valid for the period specified in the recognition letter and application for renewal of recognition shall be submitted in the prescribed proforma at least 3 months before the expiry of the valid recognition. Failure to submit application in time may lead to automatic lapsing of the registration & recognition.

   ***However, the certificate of registration is not issued to R&D units of companies engaged in activities falling within the definition of 'hospital' as per notification No. 24/2007-Cus dt. 01.03.2007 and No.16/2007-central excise dt. 01.03.2007 issued by Department of Revenue.*

3. The recognition given by DSIR, Ministry of Science & Technology is not transferable.
   - In case there is a change in the location of R&D unit(s), the company should intimate DSIR forthwith returning the original documents along with a request to issue amended recognition letter and registration certificate, mentioning the new address.
   - In case there is the change in the name of the company, it should intimate DSIR forthwith returning the original documents along with a request to issue amended recognition letter and registration certificate, mentioning the new name.

4. In case of merger/de-merger/amalgamations, the department should be intimated immediately.The company should also spell out/reiterate its policy towards R&D and submit an undertaking to continue the R&D activities, budgets, staffing, etc. along with necessary documents including legal documents such as court orders, ROC certificate/returns, if any, within one month failing which the company should apply for fresh recognition.

5. Separate accounts shall be maintained for each R&D unit and the consolidated expenditures shall be reflected in the audited statement of accounts in the Annual Report.

6. The company should submit a copy of its Annual Report within 15 days of its publication, along with annual return containing brief summary of achievements of the R&D unit(s), new products developed, process developed/introduced, patents filed/granted, papers published, award and prizes received and any other achievements to DSIR at the end of every year.

7. Commercial exploitation of the know-how/process developed by the in-house R&D unit(s) will be solely governed by the licensing policies of the Government, in operation from time to time and the decision of the licensing authorities.

8. DSIR Recognition to In-house R&D unit(s) should not in any way be construed as approval for introduction of products/technologies developed in the R&D units, In the market. Companies shall obtain all necessary statutory and type approvals from the appropriate from the appropriate government authorities before introduction and /or marketing of the products /technologies. DSIR will not be responsible in any way for non-compliance of this,by the companies.

9. The recognition by DSIR does not amount to approval under any section of Income Tax Act. Tax concessions, rebates, import concessions etc, if any, will be governed by the tax laws in operation from time to time. All such matters should be taken up by the company directly with the concerned authorities.

10. The registration will entitle the In-house R&D units to avail of customs/excise duty exemption on purchase of equipment, instruments, spares thereof, consumables etc. used for research and development subject to relevant Government policies in force from time to time. Such exemptions will have to be separately applied for in the prescribed formats. The R&D units should also abide by the terms & conditions of the customs & central excise notifications issued/amended from time to time.

11. Disposal/sale of equipment and products/prototypes/intermediates, if any, emanating from the R&D/priot plant, should be intimated to DSIR immediately. The realization if any, from services rendered, disposal of above shall be shown in the R&D accounts of the firm as well as tax returns, as income of R&D unit. In case of disposal/sale of R&D equipment, clearance from customs/excise authorities will also be required in view of the applicable notifications under which the equipment was Imported/purchased in India.

12. Any violation of the terms & conditions mentioned above and/or provisions of taxation in force will make the firm liable to de-recognition.

13. The company will also conform to such other conditions for recognition stipulated in the Guidelines or as may be specifically provided in the recognition letter.

*****

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The Federation Of Andhra Pradesh Chambers Of Commerce & Industry

(An ISO 9001:2000 Certified Organisation)

Award for 2005 - 2006

Excellence in Research and Development
(Small Scale Industry)
(Silver Rolling Trophy) - Instituted by Elico Ltd., Hyderabad

Presented to

Lee Pharma Ltd., Hyderabad

at the
89th ANNUAL AWARD FUNCTION
on 8th June, 2007

In recognition of their Research & Development in developing Innovative and cost effective simplified process for manufacture of Flumazenil, Anhydrous Olanzapine Form I and Clopidogrel Bisulfate Form I.

SUDHIR SANGHI
PRESIDENT

O.P. GOENKA
CHAIRMAN, AWARDS COMMITTEE

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ANNEXURE-R

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LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Under campagin

	Products/ Therapeutic category	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
Antihypertensive			
1	Valsartan	In-House	Tech. Pack available
2	Olmesartan	In-House	Tech. Pack available
3	Azilsartan	In-House	Tech. Pack available
4	Telmisartan	In-House	Tech. Pack available
Antiosteoporosis			
5	Strontium Ranelate	In-House	Tech. Pack available
Antipsychotic			
6	Aripiprazole	In-House	Tech. Pack available
7	Levosulpiride	In-House	Tech. Pack available
Antidepressant			
8	Vilazodone HCl	In-House	Tech. Pack available
Anticonvulsant			
9	Lacosamide	In-House	Tech. Pack available
Antibacterial			
10	Prulifloxacin HCl	In-House	Tech. Pack available
Antispasmodic			
11	Trospium Chloride	In-House	Tech. Pack available
Antihistaminic			
12	Azelastine	In-House	Tech. Pack available

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LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Regular/Commercial

#	Therapeutic products	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
Hyper Lipidemic/ HMG- COA reductase			
1	Atorvastatin Calcium	IP	CTD compiled
		EP/USP	Technical Package available
2	Rosuvastatin Calcium	IP	CTD available as per IP
		ICH/ Ph-Eur	Technical Package available
Antihypertensive			
3	S- Amlodipine Besylate	IDL-CHINA	CTD compiled
4	S - Amlodipine Maleate	IDL-CHINA	CTD compiled
5	Enalaprilat	In-House	Tech. Pack available
6	Cilnidipine	In-House	Tech. Pack available
Antiplatetelet			
7	Clopidogrel Bisulfate Form I	USP	CTD compiled
8	Clopidogrel Bisulfate Form II	USP	Tech. Pack available
9	Prasugrel HCL	In-House	Tech. Pack available
Antiulcerative			
10	Omeprazole	EP	CEP available
11	Omeprazole Sodium	EP	Tech. Pack available
12	Omeprazole Magnesium	EP	CTD filed
		USP	Tech. Pack available
13	Esomeprazole Sodium	ICH	CTD compiled
14	Esomeprazole Magnesium Trihydrate	EP	CTD compiled
15	Esomeprazole Magnesium Dihydrate	ICH	CTD compiled
16	Lansoprazole	EP/USP	CEP available
17	DexLansoprazole	ICH	Tech. Pack available
18	Pantoprazole Sodium Sesquihydrate	EP	CEP Available
		USP	Tech. Pack available
19	Pantoprazole Magnesium Dihydrate	ICH	CTD compiled
20	Rabeprazole Sodium	In-House/Ph-Eur	CTD compiled
Anticonvulsant			
21	Pregabalin	ICH /Ph-Eur	CTD compiled
Antiosteoporosis			
22	Ibandronate Sodium	In-House/ USP	CTD compiled
23	Residronate Sodium	In-House/ USP	CTD compiled
Antipsychotic			
24	Olanzapine Form I	In-house/EP/USP	CTD Filed
25	Olanzapine Form II	EP	Tech. Pack available
26	Olanzapine Form V	USP	CTD compiled

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LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Regular/Commercial

#	Therapeutic products	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
27	Asenapine Maleate	In-House	CTD compiled
28	Lurasidone Hydrochloride	In-House	Tech. Pack available
Antifungal			
29	Itraconazole	EP	CEP available
30	Voriconazole	EP	CEP Filed
31	Terconazole	In-House	CTD compiled
Antihistaminic			
32	Cetrizine dihydrochloride	EP	CTD is under compilation
33	Levocetrizine Dihydrochloride	IP	CTD compiled
34	Montelukast Sodium	IP/EP/USP	Tech. Pack available
Antidepressant			
35	Duloxetine HCl	EP	CTD is under compilation
36	Sertraline HCl	EP	CTD compiled
37	Sertraline HCl Form I	EP	Tech. Pack available
38	Sertraline HCl Form II	EP	CTD Filed
39	Venlafaxine HCl	EP	CTD Filed
40	DesVenlafaxine Succinate	In-House	Tech. Pack available
Antibacterial			
41	Linezolid Form II	In-House	CTD is under compilation
42	Moxifloxacin HCl	EP/USP	CTD is under compilation
Overactive Bladder			
43	Fesoterodine Fumarate	In-House	Tech. Pack available
Benign Prostatic Hypertrophy			
44	Tamsulosin HCl	EP	CTD compiled
Anti Coagulant			
45	Dabigatran Etexilate mesylate	In-House	Tech. Pack available
Premature Ejaculation			
46	Dapoxetine Hcl	In-House	Tech. Pack available
Anti-Inflammatory (NSAID)			
47	Etoricoxib	In-House	Tech. Pack available
Anti-gout			
48	Febuxostat	In-House	Tech. Pack available

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LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
1	2-chloromethyl-3-methyl-4- (2,2,2-trifluoroethoxy) pyridine hydrochloride (Lansoprazole chloro compound)	Lansoprazole	127337-60-4
2	2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridine-2-yl] methyl]thio]-1H-benzimidazole (Lansoprazole Sulphide compound)	Lansoprazole	103577-40-8
3	2-(Chloromethyl)-3,4-dimethoxy pyridine hydrochloride (Pantoprazole Chloro Compound)	Pantoprazole sodium	72830-09-2
4	5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl] thio]-1H-benzimidazole (Pantoprazole Sulphide compound)	Pantoprazole sodium	102625-64-9
5	2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] thio]-1H-benzimidazole (Rabeprazole Sulphide compound)	Rabeprazole	117977-21-6
6	Cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan -4-yl] methanol-p-Toluenesulfonate	Terconazole Itraconazole	103661-14-9
7	4-(4-Hydroxy phenyl)-1-(1-methylethyl)piperazine	Terconazole	67914-97-0
8	(R*,S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidine-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol	Voriconazole	188416-29-7
9	2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoro pyrimidine-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol hydrochloride	Voriconazole	188416-35-5
10	(S)-3-(dimethylamino)-1-(thiophen-2-yl) propan-1-ol-2-hydroxy-2-phenylacetate	Duloxetine Hydrochloride	287737-72-8
11	2-(2-Nitro anilino)-5-methyl thiophene-3-carbonitrile	Olanzapine	138564-59-7
12	4-amino-2-methyl-10H-thieno [2,3-b] [1,5] benzodiazepine hydrochloride	Olanzapine	138564-60-0
13	7-(4-bromo butoxy)-3,4-dihydro carbostyril	Aripiprazole	29722-34-5
14	(R)-5-(2-aminopropyl)-2-methoxy-benzenesulfonamide	Tamsulosin HCl	112101-81-2
15	1-(2-bromoethoxy)-2-ethoxy-benzene	Tamsulosin HCl	3259-03-8
16	(R)-5-bromo-3-[(1-methyl-2-pyrrolidinyl)methyl]-1H-indole	Eletriptan	143322-57-0
17	2-Bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone	Prasugrel	204205-33-4
18	Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester	Fesoterodine Fumerate	156755-35-0
19	(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine	Fesoterodine Fumerate	207679-81-0
20	N-[3-amino-4-(methylamino)benzoyl]-N-2-pyridinyl-, ethyl ester	Dabigatran	212322-56-0
21	2-(n-Butyl)-3-(4-hydroxybenzoyl)-5-nitrobenzofuran	Dronedarone	141645-16-1
22	Methyl 2-[1-[[(benzyloxy)carbonyl]amino]-1-methylethyl]-5,6-dihydroxypyrimidine-4-carboxylate	Raltegravir	519032-08-7
23	Methyl 2-[1-[[(benzyloxy)carbonyl]amino]-1-methylethyl]-1-Methyl-5-Hydroxy-6-Oxo-1,6-dihydroxypyrimidine-4-carboxylate	Raltegravir	888504-27-6
24	Benzyl [1-[4-[[(4-Fluorobenzyl]amino]carbonyl]-5-Hydroxy-1-Methyl-6-Oxo-1,6-Dihydropyrimidine-2-yl]-1-Methylethyl]Carbamate	Raltegravir	518048-02-7
25	5-Methyl-1,3,4-Oxadiazole-2-Carboxylic Acid Potassium Salt	Raltegravir	888504-28-7
26	(1S,3S,5S)-3-(Aminocarbonyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester	Saxagliptan	361440-67-7

LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
27	(1S,3S,5S)-2-Azabicyclo[3.1.0]hexane-3-carboxamide	Saxagliptan	361440-68-8
28	(1S,3S,5S)-2-Azabicyclo[3.1.0]hexane-3-carboxamide, 2,2,2-trifluoroacetate (1:1)	Saxagliptan	361440-69-9
29	(aS)-a-[[(1,1-dimethylethoxy)carbonyl]amino]-3-hydroxytricyclo[3.3.1.13,7]decane-1-acetic acid	Saxagliptan	361442-00-4
30	3-(1-Piperazinyl)-1,2-Benzisothiazole	Lurasidone	87691-87-0
31	(3aR,4S,7R,7aS) 4,7-Methano-1H-isoindole-1,3(2H)-dione	Lurasidone	14805-29-9
32	(R,R) Cyclohexane Dicarboxylic Acid	Lurasidone	46022-05-3
33	(3aR, 7aR)-Hexahydroisobenzofuran-1,3-Dione	Lurasidone	71749-03-6
34	2,3,4,5-Tetrahydro-3-(Trifluoroacetyl)-1,5-Methano-1H-3-Benzazepine	Varenicline	230615-51-7
35	2,3,4,5-Tetrahydro-1,5-Methano-1H-3-Benzazepine Hydrochloride	Varenicline	230615-52-8
36	8-Bromo-7-(But-2-ynyl)-3-Methyl-1H-Purine-2,6(3H,7H)-Dione,	Linagliptin	666816-98-4
37	3-(R)-Piperdinyl Pthalimide Hydrochloride	Linagliptin	886588-61-0
38	(R)-Tert-Butyl piperdin-3-yl Carbamate	Linagliptin	309956-78-3
39	1-(Isobutyloxy)ethyl-4-Nitrophenyl Carbonate	Gabapentin	NA
40	(1R,2S,5S)-6,6-Dimethyl-3-Aza-Bicyclo[3.1.0]Hexane-2-Carboxylic Acid Methyl Ester Hydrochloride	Boceprevir	565456-77-1
41	Beta-Amino-Alpha-Hydroxycyclobutanebutanamide Hydrochloride	Boceprevir	394735-23-0
42	N-[(1,1-dimethylethoxy)carbonyl]-3-methyl-L-valine	Boceprevir	62965-35-9
43	1-[N-(2,6-Dimethylphenyl)carbomylmethyl]piperazine	Ranolazine	5294-61-1
44	(2-methoxyphenoxy)-2,3-Epoxypropane	Ranolazine	2210-74-4
45	3-(4-chlorobutyl)-1H-indole-5-carbonitrile	Vilazodone	143612-79-7
46	Ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate	Vilazodone	163521-20-8
47	4-Oxo-1,4-Dihydroquinoline-3-Carboxylic Acid	Ivacaftor	13721-01-2
48	5-Amino-2,4-Di-Tert-Butylphenyl methyl carbonate	Ivacaftor	1182822-31-6
49	2-Chloromalonaldehyde	Etoricoxib	36437-19-1
50	1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl] Ethanone	Etoricoxib	221615-75-4
51	4-amino-1- ((2R,3R,4R,5R)-3- fluoro-4-hydroxy-5- (hydroxymethyl)-3-methyltetrahydrofuran- 2-yl)pyrimidin-2(1H)-one	Sofusbuvir	817204-33-4
52	1-(4- iodophenyl) – piperidine -2- one	Apixaban	385425-15-0
53	Chloro (4- methoxyphenyl) hydrazono) acetic acid ethyl ester	Apixaban	27143-07-3
54	2- Piperiodone	Apixaban	675-20-7
55	(S,S)-2,8-Diazabicyclo[4,3,0] nonane	Moxifloxacin Hydrochloride	151213-40-0
56	1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid ethyl ester	Moxifloxacin Hydrochloride	112811-71-9

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LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
57	(2-[2-[3(S)-[3-[(1E)-2-(7-chloroqunolin-2-yl)phenyl]-3-hydroxypropyl]phenyl-2-propanol)	Montelukast sodium	142569-70-8
58	(1-(Mercaptomethyl) cyclopropane acetic acid)	Montelukast sodium	162515-68-6

LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

ENTERIC COATED / DELAYED RELEASE PELLETS	DMF STATUS
Omeprazole	DMF Filed
Lansoprazole	DMF Filed
Esomeprazole Magnesium Trihydrate	DMF Filed
Esomeprazole Magnesium Dihydrate	T/P available
Rabeprazole Sodium	DMF Filed
Pantoprazole Sodium	DMF Compiled
Diclofenac Sodium	T/P available
Diclofenac Potassium	T/P available
Mebeverine Hcl	DMF Compiled
Duloxetine HCl	T/P available
Aspirin	DMF Filed
Omeprazole + Domperidone	T/P available
Lansoprazole + Domperidone	T/P available
Pantoprazole + Domperidone	T/P available
Rabeprazole + Domperidone	T/P available
Clopidogrel + Aspirin	T/P available
Prasugrel + Aspirin	T/P available
Dexlansoprazole	T/P available
IMMEDIATE RELEASE PELLETS	**DMF STATUS**
Itraconazole	DMF Filed
Orlistat	DMF Filed
Domperidone	T/P available
Folic Acid	T/P available
Levocetirizine Di HCl	T/P available
Cetirizine HCl	T/P available
Atorvastatin	T/P available
Ferrous Ascorbate	T/P available
Mebeverine Hcl	T/P available
Fenofibrate	DMF Compiled
Secnidazole	T/P available
Prasugrel	T/P available
Rosuvastatin Calcium	T/P available
SUSTAINED RELEASE PELLETS	**DMF STATUS**
Venlafaxine Hcl	DMF Compiled
Diltiazem Hcl	T/P available
Indomethacin	T/P available
Itopride	T/P available
Tamsulosin Hcl	DMF Compiled
Mebeverine Hcl	DMF Compiled

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LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

SUSTAINED RELEASE PELLETS	DMF STATUS
Metoprolol Succinate	CTD compiled
Propranolol	T/P available
Pseudophedrine	T/P available
Diclofenac Sodium	T/P available
Diclofenac Potassium	T/P available
Domperidone	DMF Compiled
Fenofibrate	T/P available
Ambroxol	T/P available
Nifedipine	T/P available
Trimetazidine	T/P available
Theophylline	T/P available
Tizanidine	T/P available
Aceclofenac	T/P available
Cinitapride	T/P available
Desvenlafaxine	T/P available

SUSTAINED RELEASE PELLETS	DMF STATUS
Isosorbide Dinitrate	T/P available
Isosorbide Mononitrite	T/P available
Isoxsuprine hcl	T/P available
Ferrous Fumarate	T/P available
Ascorbic acid	T/P available
Dried Ferrous Sulphate , Zinc Sulphate monohydrate & Folic Acid	T/P available
Atorvastatin + Fenofibrate	T/P available
Galanthamin Hydrobromide	T/P available
Cyclobenzaprine HCl	T/P available
Minocycline HCl	T/P available
Trospium Chloride	T/P available
Nicardipine HCl	DMF Compiled
Phenylephrine HCl	T/P available
Fesoterodine fumarate	T/P available
Caffeine	T/P available
Pseudoephidrine + Loratidine	T/P available
Dipyridamole	T/P available
Chloropheniramine Maleate	T/P available
Carvedilol Phosphate	T/P available
Mesalamine	T/P available

MULTIPLE UNIT PELLETS (MUPS)	DMF STATUS
Omeprazole	T/P available
Lansoprazole	T/P available
Esomeprazole Mg. Trihydrate	T/P available
Esomeprazole Mg. Dihydrate	T/P available

IPO MUMBAI 29-06-2015 16:01

LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

TASTE - MASKED GRANULES FOR SUSPENSION	DMF STATUS
Omeprazole	T/P available
Esomeprazole Magnesium	T/P available
Azithromycin	T/P available
Clarithromycin	T/P available
Roxithromycin	T/P available
Ciprofloxacin	T/P available
Ibuprofen	T/P available
DIRECTLY COMPRESSIBLE GRANULES	**DMF STATUS**
Atorvastatin	T/P available
Simvastatin	T/P available
Atorvastatin + Fenofibrate	T/P available
Simvastatin + Fenofibrate	T/P available
Ciprofloxacin	T/P available
Atorvastatin+ Ezetimibe	T/P available
Clopidogrel + Aspirin	T/P available

IPO MUMBAI 29-06-2015 16:01

ANNEXURE-S

Certificate of Registration

nqa.

This is to certify that the Quality Management System of

Lee Pharma Limited
Office: Sy. No. 257 & 258/1, Door No. 11-6/56-C, Opp. IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad - 500 037, Andhra Pradesh, India
Factory: 10/G-1, Gaddapotharam Village, Jinnaram Mandel, Medak District - 502 319, Andhra Pradesh, India

applicable to

Manufacturing, supply and sale of intermediate chemicals and active pharmaceuticals ingredients

has been assessed and registered by NQA against the provisions of

BS EN ISO 9001 : 2008

This registration is subject to the company maintaining a quality management system, to the above standard, which will be monitored by NQA.

Certification Director

Certificate No:	18461
Date:	23 September 2004
Reissued:	28 August 2013
Valid Until:	28 August 2016
EAC Code:	13

UKAS QUALITY MANAGEMENT
015

The use of the UKAS Accreditation Mark indicates accreditation in respect of those activities covered by the accreditation certificate number 015 held by NQA.
NQA is a trading division of Ascertiva Group Ltd; Registration No. 02513162. Registered Office: Warwick House, Houghton Hall Park, Houghton Regis, Dunstable, Bedfordshire, LU5 5ZX.
This certificate is the property of NQA and must be returned on request.

IPO MUMBAI 29-06-2015 16:03

Certificate of Registration

nqa

This is to certify that the Environmental Management System of

Lee Pharma Limited
Office: Sy No. 257 & 258/1, Door No: 11-6/56-C, Opp: IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad – 500 037, India
Factory: 10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District – 502 319, A.P, India

applicable to

Manufacture, testing, packaging and sale of intermediate chemicals and active pharmaceutical ingredients

has been assessed and registered by NQA against the provisions of

BS EN ISO 14001 : 2004

This registration is subject to the company maintaining an environmental management system, to the above standard, which will be monitored by NQA.

Certificate No: E 3326
Date: 14 September 2009
Reissued: 30 August 2012
Valid Until: 30 August 2015

Certification Director

UKAS ENVIRONMENTAL MANAGEMENT 015

The use of the UKAS Accreditation Mark indicates accreditation in respect of those activities covered by the accreditation certificate number 015 held by NQA.
NQA is a trading division of Ascotiva Group Ltd. Registration No. 02513162. Registered Office: Warwick House, Houghton Hall Park, Houghton Regis, Dunstable, Bedfordshire, LU5 5ZX.
This certificate is the property of NQA and must be returned on request.

IPO MUMBAI 29-06-2015 16:03

Danish Health and Medicines Authority

CERTIFICATE NUMBER: ***DK API-H 00056615***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Denmark confirms the following:
The manufacturer: ***Lee Pharma***
Site address: ***Survey No. 10/G-1, Gaddapotharam, Kazipally Industrial Estate, Jinnaram (Mandal), Medak district, Andhra Pradesh, 502319, India***

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC .

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-02-21*** , it is considered that it complies with :

- The principles of GMP for active substances [3] referred to in Article 47 of Directive 2001/83/EC .

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMP. If it does not appear, please contact the issuing authority.

---

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

IPO MUMBAI 29-06-2015 16:03

Part 2

Manufacture of active substance. Names of substances subject to inspection :
LANSOPRAZOLE(en)
PANTOPRAZOLE SODIUM SESQUIHYDRATE(en)
OMEPRAZOLE(en)

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : LANSOPRAZOLE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Micronisation 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing
Active Substance : PANTOPRAZOLE SODIUM SESQUIHYDRATE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Micronisation 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing
Active Substance : OMEPRAZOLE	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.1 Manufacture of active substance intermediates

IPO MUMBAI 29-06-2015 16:03

	3.1.2 Manufacture of crude active substance
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Micronisation 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing

2015-05-12

Name and signature of the authorised person of the Competent Authority of Denmark

Mr. Claus Mortensen
Danish Health and Medicines Authority
Tel: ***+45 44 889237***
Fax: ***+45 44 889195***

IPO MUMBAI 29-06-2015 16:03

Danish Health and Medicines Authority

CERTIFICATE NUMBER: ***DK H 00056815***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Denmark confirms the following:
The manufacturer: ***Lee Pharma Limited*** □ ***Site II***
Site address: ***Vsez, Duvvada, Vishakapatnam, AP, 530049, India***

Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 111(4) of Directive 2001/83/EC .

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-02-24*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMP. If it does not appear, please contact the issuing authority.

---

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

IPO MUMBAI 29-06-2015 16:03

Part 2

Human Medicinal Products

1 MANUFACTURING OPERATIONS	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.17 Other: Manufacture of pellets(en)
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

Clarifying remarks (for public users)

Manufacture of Itraconazole pellets 22%, Lansoprazole pellets 8.5% and Omeprazole pellets 8.5% covered by the inspection

2015-05-12

Name and signature of the authorised person of the Competent Authority of Denmark

Mr. Claus Mortensen
Danish Health and Medicines Authority
Tel: ***+45 44 889237***
Fax ***+45 44 889195***

IPO MUMBAI 29-06-2015 16:03

302

SALUD
SECRETARÍA DE SALUD

Cofepris
Comisión Federal para la Protección contra Riesgos Sanitarios

ESTADOS UNIDOS MEXICANOS
COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS
COMISIÓN DE AUTORIZACIÓN SANITARA
SUBDIRECCIÓN EJECUTIVA DE LICENCIAS SANITARIAS

"2013, Año de la Lealtad Institucional y Centenario del Ejercito Mexicano"

CERTIFICADO No. 133300CI110227

México, D.F. a 10 de Septiembre de 2013

LEE PHARMA LIMITED
Por conducto de su representante legal o apoderado legal
o quien legalmente represente sus derechos.
Plot No. V, Phase II, Vsez, Duvvada,
Sabbavaram (Mandal) Visakhapatnam District,
Andhra Pradesh, India.
PRESENTE

Con fundamento en los artículos 4° párrafo cuarto, 8 y 14 de la Constitución Política de los Estados Unidos Mexicanos; 39 de la Ley Orgánica de la Administración Pública Federal; 1, 3 y 16 fracción X de la Ley Federal del Procedimiento Administrativo; 3 fracciones XXIV y XXVI, 4 fracción III, 17 bis fracción V, 194, 197 287, 388, 389 fracción V, 391 bis y 392 de la Ley General de Salud; 1 y 2 inciso c fracciones X del Reglamento Interior de la Secretaría de Salud; 1, 3 fracción I inciso b y VI, 4 fracción II inciso c y 14 fracción IX del Reglamento de la Comisión Federal para la Protección contra Riesgos Sanitarios; 1, 167 fracción VI, 170 fracción II, 190 bis 1 fracción VI, 190 bis 2 fracción III, 190 bis 3 fracción VI, 190 bis 4 fracción II, 208 del Reglamento de Insumos para la Salud modificado el 02 de enero de 2008; vigésimo primero del Acuerdo por el que se modifica el diverso por el que se delegan las facultades que se señalan, en los órganos administrativos que en el mismo se indican de la Comisión Federal para la Protección contra Riesgos Sanitarios, Publicado en el Diario Oficial de la Federación el 7 de abril de 2010 y el 23 de marzo de 2012; así como los relativos y aplicables del Acuerdo por el que se modifica el diverso por el que se dan a conocer los trámites inscritos en el Registro Federal de Trámites Empresariales que aplica la Secretaría de Salud y se establecen diversas medidas de mejora regulatoria y por el que se dan a conocer los formatos para la realización de trámites que aplica la Secretaría de Salud, a través de la Comisión Federal para la Protección Contra Riesgos Sanitarios, publicado el 23 de octubre de 2012 en el Diario Oficial de la Federación; y por medio del presente se hace constar que la **empresa citada al rubro, clasificada como Fabrica o Laboratorio de Materias Primas para la Elaboración de Medicamentos o Productos Biológicos para uso Humano, cuenta con Licencia Sanitaria No. 33/VP/AP/2010/F/G, cumple con las Buenas Prácticas de Fabricación exigidas por las Autoridades Sanitarias en México, conforme a la Legislación Sanitaria Vigente en la materia y sus instalaciones están sujetas a verificación por parte de esta Comisión Federal, por lo que está autorizada para fabricar los siguientes productos obtenidos por síntesis química, desde el principio activo hasta su presentación comercial en pellets:**

- **Venlafaxina HCl SR Pellets 33% y Tamsulosina HCl SR Pellets 0.2%, en presentación de cuñetes de plástico de 25.00 Kg.**

Se expide el presente Certificado a petición del interesado para los fines legales a que haya lugar, el cual vence el dia 0[illegible] de 2016, pero al modificar las condiciones en que fue otorgado o presentar desviaciones el Certificado queda sin efecto.

SUBDIRECTOR EJECUTIVO DE LICENCIAS SANITARIAS

MARCOS LAUREANO SOLIS LEYVA

SECRETARÍA DE SALUD
COMISION FEDERAL DE PROTECCION CONTRA RIESGOS SANITARIOS
SUBDIRECCION EJECUTIVA DE LICENCIAS SANITARIAS

En el ejercicio de la facultad delegada en el artículo Vigésimo Primero del Acuerdo por el que se modifica el diverso por el que se delegan las facultades que se señalan, en los órganos administrativos que en el mismo se indican de la Comisión Federal para la Protección contra Riesgos Sanitarios. Publicado en el Diario Oficial de la Federación el 7 de abril de 2010 y el 23 de marzo de 2012.

c.c.p. Expediente de la Comisión de Autorización Sanitaria, 1° Piso.

IVCB/NEST 09.09.13 SLS/04/0384/2013 CBPF FIN TD

COF 002037

Oklahoma No. 14, Col. Nápoles, Del. Benito Juárez, D.F., C.P. 03810
Tel. 5080-5200 (Ext.1366) 01 800 033 50 50 www.cofepris.gob.mx

Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subd

CAS-SELS

IPO MUMBAI 29-06-2015 16:03

GOVERNMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION

** ** **

Office of the Designated Officer &,
Deputy Director,
Drugs Control Administration,
Vengalraonagar,
Hyderabad – 500 038.

L.Dis.No.4484/A3/2014 Dated 27-10-2014.

G.M.P. CERTIFICATE

This is to certify that **M/s. LEE PHARMA LIMITED,** situated at Sy.No.10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District is holding Drug Manufacturing Licence in Form – 25 bearing No. **35/MD/AP/2000/B/CC** dated 06.06.2000, valid upto 13.09.2015 for manufacture for sale or distribution of the drugs approved to them by this department. The firm is subjected to periodical inspection by this Department.

The firm is following **GOOD MANUFACTURING PRACTICES** as stipulated under the provisions of **SCHEDULE 'M'** of Drugs and Cosmetics Rules, 1945.

The firm should, however carryout self-inspection from time to time to ensure that the requirements of Good Manufacturing Practices are complies with.

This certificate is issued as requested by the firm for registering the drugs to various countries.

This certificate is valid for one year from the date of issue.

27/10/14

DEPUTY DIRECTOR & CERTIFYING AUTHORITY
DRUGS CONTROL ADMINISTRATION

To

M/s. LEE PHARMA LIMITED,
Sy.No.10/G-1, Gaddapotharam Village,
Jinnaram Mandal, Medak District.

IPO MUMBAI 29-06-2015 16:03

GOVERNMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION
** ** **

L.Dis.No.175/A3/2014. Dated 10 - 10 - 2014.

From

R. UDAY BHASKAR,
Designated Officer(I/c) & Assistant Director,
Licensing Authority & Controlling Authority,
Drugs Control Administration,
Vengalraonagar,
Hyderabad.

To

M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1,
Gaddapotharam Village,
Jinnaram Mandal,
Medak District,
Telangana, INDIA.

Sirs,

Sub: Drugs and Cosmetics Act, 1940 and Rules made thereunder – Issue of World Health Organization Good Manufacturing Practice Certificate – Regarding.

Ref: 1. Your application dated 04.06.2014.
2. Joint Inspection Report dated 23.09.2014 & 24.09.2014.

@@@

I forward herewith **WORLD HEALTH ORGANIZATION GOOD MANUFACTURING PRACTICE CERTIFICATE** for the products recommended by the Joint Inspection Team consisting of officers of Central Drugs Standard Control Organization and officer from Drugs Control Administration, Telangana for **Export** Purpose.

This Certificate is valid for a period of **Two** years from the date of issue.

Yours faithfully,

10/10/2014

DESIGNATED OFFICER(I/c) & ASSISTANT DIRECTOR
LICENSING AUTHORITY & CONTROLLING AUTHORITY
DRUGS CONTROL ADMINISTRATION

Deputy Director (Enforcement) ★ Drugs Control Administration HYDERABAD Government of Telangana ★ Designated Officer for Telangana

IPO MUMBAI 29-06-2015 16:03

GOVERNAMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION
** ** **

Office of the Designated Officer &
Deputy Director,
Drugs and Control Administration,
Vengalraonagar, Hyderabad – 500 038.

L.Dis.No.175/A3/2014 Dated 10 -10-2014.

LIST OF PRODUCTS APPROVED UNDER WHO GMP CERTIFICATION SCHEME FOR EXPORT PURPOSE

1.	OMEPRAZOLE	USP/BP
2.	ITRACONAZOLE	BP
3.	LANSOPRAZOLE	USP
4.	OLANZAPINE	IHS
5.	ESOMEPRAZOLE MAGNESIUM TRIHYDRATE	Ph.Eur.
6.	SERTRALINE HYDROCHLORIDE	Ph.Eur.
7.	RABEPRAZOLE SODIUM	IH
8.	ENALAPRIL MALEATE	USP
9.	CLOPIDOGREL BISULPHATE	USP
10.	PANTOPRAZOLE SODIUM	USP
11.	RESIDRONATE SODIUM	IH
12.	OMEPRAZOLE MAGNESIUM	Ph.Eur.
13.	PREGABALIN	IH
14.	AMLODIPINE BESYLATE	BP/Ph.Eur.
15.	VORICONAZOLE	IHS
16.	ROSUVASTATIN CALCIUM	IH
17.	MOXIFLOXACIN HYDROCHLORIDE	BP/Ph.Eur.
18.	DULOXETIN HYDROCHLORIDE	IH
19.	TAMSULOSIN HYDROCHLORIDE	IP/IH
20.	VENLAFAXIN HYDROCHLORIDE	Ph.Eur.
21.	MONTELUKAST SODIUM	IP/Ph.Eur.
22.	ATORVASTATIN CALCIUM	IP/USP
23.	DESVENLAFAXINE SUCCINATE	IH
24.	ESOMEPRAZOLE SODIUM	IH

Manufacturer : M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1,
Gaddapotharam Village,
Jinnaram Mandal, Medak District,
Telangana, INDIA.

When applicable : Placing the products on the market as detailed above.

Deputy Director (Enforcement) ★ Designated Officer for Telangana ★ Drugs Control Administration Government of Telangana HYDERABAD

10/10/2014

IPO MUMBAI 29-06-2015 16:03

L.Dis.No.175/A3/2014:

WHO GMP CERTIFICATE Issued to M/s. LEE PHARMA LIMITED, Sy.No. 10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District, Telangana, INDIA

** ** **

It is certified that these products had been authorized to be placed on the market for use in the country and exporting countries.

Drug Licence No. : **35/MD/AP/2000/B/CC**, dated 06.06.2000, in Form – 25.

The Unit of M/s. LEE PHARMA LIMITED, Sy.No. 10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District, Telangana, INDIA was inspected by Mrs. P. Indira, Drugs Inspector, O/o the Deputy Drugs Controller(India), CDSCO, Zonal Office, Hyderabad and Sri. K. Anil Kumar, Drugs Inspector, Drugs Control Administration, Hyderabad on 23.09.2014 and 24.09.2014.

The manufacturer conforms to requirement for **Good Manufacturing Practices** in the manufacturing and quality control (As recommended by the **World Health Organization**) in respect of the products mentioned above (**TWENTY FOUR** in number) for Export in the international market.

This certificate is valid for a period of **Two** years from the date of issue.

Deputy Director (Enforcement) ★ Designated Officer for Telangana ★ Drugs Control Administration HYDERABAD Government of Telangana

10/10/2014

DESIGNATED OFFICER(I/c) & ASSISTANT DIRECTOR
LICENSING AUTHORITY & CONTROLLING AUTHORITY
DRUGS CONTROL ADMINISTRATION

To
M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1, Gaddapotharam Village,
Jinnaram Mandal, Medak District,
Telangana, INDIA.

IPO MUMBAI 29-06-2015 16:03

GOVERNMENT OF ANDHRAPRADESH
DRUGS CONTROL ADMINISTRATION

From
T.Ravi Kumar
Deputy Director,
Drugs Control Administration,
Visakhapatnam Region,
Visakhapatnam

To
M/s Lee Pharma Limited,
Plot No.V, Phase-II, VSEZ,
Duvvada, Sabbavaram (M),
Visakhapatnam District.

Rc. No. 160 /DD/DCA/VSP/2015 Dated 08-04-2015

Sir,

Sub: Drugs and Cosmetics Act.1940 and the Rules made there under – Grant of GMP Certificate to M/s Lee Pharma Limited, Plot No.V, Phase-II, VSEZ, Duvvada, Sabbavaram(M), Visakhapatnam District – Reg.

Ref: 1. Your Application Dt. 24-01-2015, received on 24-01-2015
2. GMP Certificate Dt. 08-04-2015

With reference to your application cited, I am here with forwarding GMP Certificate No.160/DD/DCA/VSP/2015 Dt.08-04-2015, Valid up to 07-04-2016 of M/s Lee Pharma Limited, Plot No.V, Phase-II, VSEZ, Duvvada, Sabbavaram (M), Visakhapatnam District.

Yours faithfully,

8/4/2015

DEPUTY DIRECTOR
DRUGS CONTROL ADMINISTRATION
VISAKHAPATNAM REGION

DEPUTY DIRECTOR
Drugs Control Administration
Visakhapatnam

Encl: GMP Certificate Dt. 08-04-2015

Copy Submitted to the Director, DCA, Hyderabad for favour of information.

IPO MUMBAI 29-06-2015 16:03

GOVERNMENT OF ANDHRAPRADESH
DRUGS CONTROL ADMINISTRATION

Office of the Deputy Director,
Drugs Control Administration,
Visakhapatnam Region,
Visakhapatnam -530 003.

File.No.160/DD/DCA/VSP/2015 Dated: 08-04-2015

G.M.P. CERTIFICATE

This is to certify that **M/s LEE PHARMA LIMITED,** Plot No.V, Phase-II, VSEZ, Duvvada, Sabbavaram (Mandal) Visakhapatnam District is holding license in Form-25 bearing No. **33/VP/AP/2010/F/G,** Dated. 15-07-2010, Valid up to 14-07-2015 for manufacture, for sale or distribution of drugs approved by this Department. The firm is subjected to periodical Inspection by this Department.

The firm is following **GOOD MANUFACTURING PRACTICES** as stipulated under the provisions of **Schedule 'M'** of Drug and Cosmetics Rules, 1945.

The firm should however carry out self inspection from time to time to ensure that the requirements of Good Manufacturing Practices are complied with.

The Certificate is valid up to 07-04-2016.

Dy. Director DCA Govt of A.P VISAKHAPATNAM

8/4/2015

(T. RAVI KUMAR)
DEPUTY DIRECTOR & CERTIFYING AUTHORITY
DRUGS CONTROL ADMINISTRATION
VISAKHAPATNAM REGION
DEPUTY DIRECTOR
Drugs Control Administration
Visakhapatnam

To
M/s LEE PHARMA LIMITED,
Plot No.V, Phase-II, VSEZ,
Duvvada, Sabbavaram (M),
Visakhapatnam District,
Andhra Pradesh, India.

Copy submitted to the Director, Drugs Control Administration, Hyderabad for information.

IPO MUMBAI 29-06-2015 16:03

ANNEXURE-T

309

o/c

Lee Pharma Limited

CIN : U24230TG1997PLC028095

13th May, 2015

To,
The Deputy Director Designated Officer,
Controlling Authority & Licensing Authority,
Drugs control Administration,
Government of Telangana,
Vengalrao Nagar,
Hyderabad – 500 038.

Dear Sir,

Sub: Request for grant of Drug Licence for Additional products to Manufacturing on Loan Licence in Form 25-A - reg.
Ref: Our Licence No: 04/RR/TS/2014/F/G(L), Date: 17.06.2014, valid up to 16.06.2019.

****

With reference to the above, we would like to inform you that, we are holding valid drug Loan Licence cited above, now we request you to kindly grant of Drug License to Manufacture of additional product as mentioned in Form – 24 A for export and domestic purpose at the premises situated at Indu Drugs Pvt Ltd., 5-5-35/278,279 & 281/1 (part), Prasanthi Nagar, IDA Kukatpally, Hyderabad – 500 072. Andhra Pradesh.

We are enclosing herewith the following documents for your perusal and necessary approval.

1. Form 24-A duly filled and signed by us.
2. Original Challan No.20514, dt. 13.05 2015 for Rs. 1860/-
3. Specimen labels of the products
4. Analytical Specifications of above products
5. Manufacturing process of the products
6. Method of Analysis f the products
7. Flow chart of the products
8. Consent letters of Technical Staff.
9. Copy of Valid Drug Licence in Form – 25-A of Indu Drugs Pvt Ltd.

Please acknowledge the receipt of the same.

Thanking you,

Yours faithfully,
For LEE PHARMA LIMITED

S. MOHAN RAO
AUTHORISED SIGNATORY

Encl: As above

Where quality is first nature

Sy. No.: 257 & 258/1, Door No.: 11-6/56, C-Block, Opp: IDPL Factory, Moosapet, Balanagar (Posl), Hyderabad - 500 037. T.S., INDIA
Tel: 91-40-66170334 / 66170335 / 66170336 / 23770338 / 23770339
E-mail: info@leepharma.com http://www.leepharma.com Fax: 91-40- 23170330

IPO MUMBAI 29

FORM –24A

APPLICATION FOR THE GRANT OF A LOAN LICENCE [LICENCE TO MANUFACTURE FOR SALE OR FOR DISTRIBUTION] OF DRUG OTHER THAN THOSE SPECIFIED IN (SCHEDULES C, C(1) AND X)

I, I/we A. Venkata Reddy, S/o Mr. A.Nagi Reddy, Managing Director of M/s Lee Pharma Limited hereby apply for the Grant of additional products on Loan Licence to manufacture on the premises situated at 5-5-35/278,279 & 281/1 (part), Prasanthi Nagar IDA, Kukatpally, Hyderabad-50072 C/o Indu Drugs Pvt Ltd, the under mentioned drugs other than those specified in [schedules C and C (1) and X] to the Drugs and Cosmetics Rules.

2. Name of Drug (each substance to be separately specified). For Domestic and Export

1. **SAXAGLIPTIN TABLETS 2.5mg-** - For Export & Domestic

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	IHS
Equivalent to Saxagliptin	2.5mg

2. **SAXAGLIPTIN TABLETS 5.0mg-** - For Export & Domestic

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	IHS
Equivalent to Saxagliptin	5.0mg

3. **SAXAGLIPTIN 2.5mg + METFORMIN HCl ER TABLETS 1000mg** - For Export & Domestic

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	IHS
Equivalent to Saxagliptin	2.5mg
Metformin HCl	1000mg

DISSOLUTION
USP Apparatus II
RPM: 100
1000ml pH 6.8 Phosphate buffer

RELEASE PROFILE
After 1st Hour: 20.0% to 40.0%
After 3rd Hour: 45.0% to 65.0%
After 10th Hour: Not less than 85.0%

Contd.....2

LEE PHARMA LIMITED HYDERABAD

IPO MUMBAI 29-06-2015 16:03

4. SAXAGLIPTIN 2.5mg + METFORMIN HCl ER TABLETS 1000mg
- For Export

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	USP
Equivalent to Saxagliptin	2.5mg
Metformin HCl	1000mg

DISSOLUTION	**RELEASE PROFILE**
USP Apparatus II	After 1st Hour: 20.0% to 40.0%
RPM: 100	After 3rd Hour: 45.0% to 65.0%
1000ml pH 6.8 Phosphate buffer	After 10th Hour: Not less than 85.0%

5. SAXAGLIPTIN 5.0mg + METFORMIN HCl ER TABLETS 500mg
- For Export & Domestic

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	IHS
Equivalent to Saxagliptin	5.0mg
Metformin HCl	500mg

DISSOLUTION	**RELEASE PROFILE**
USP Apparatus II	After 1st Hour: 20.0% to 40.0%
RPM: 100	After 3rd Hour: 45.0% to 65.0%
1000ml pH 6.8 Phosphate buffer	After 10th Hour: Not less than 85.0%

6. SAXAGLIPTIN 5.0mg + METFORMIN HCl ER TABLETS 500mg
- For Export

Each Film Coated Tablet contain	
Contain: Saxagliptin Hydrochloride	USP
Equivalent to Saxagliptin	5.0mg
Metformin HCl	500mg

DISSOLUTION	**RELEASE PROFILE**
USP Apparatus II	After 1st Hour: 20.0% to 40.0%
RPM: 100	After 3rd Hour: 45.0% to 65.0%
1000ml pH 6.8 Phosphate buffer	After 10th Hour: Not less than 85.0%

3. The names, qualifications and experience of the expert staff actually connected with the manufacturer and testing of the specified products in manufacturing premises.

Approved Technical Staff of Indu Drugs Pvt Ltd

4. A fee of Rs. 1800 (Rupees One Thousand Eight hundred only) has been credited to Government under the Head of Accounts 0210-Medical and Public Health. 04 Public Health. 104 Fees Fines etc. Vide Original Challan No. 2054, dated. 13.05.2015

Place: Hyderabad
Date:

For LEE PHARMA LIMITED

VENKATA REDDY .A
MANAGING DIRECTOR

LEE PHARMA LIMITED

IPO MUMBAI 29-06-2015 16:03

Lee Pharma Limited
AN ISO 9001:2008, ISO 14001: 2004, EU GMP & WHO GMP
100% E O U

May 02, 2014

M/S Astra Zeneca AB
SE-151 85, Sodertalje
Sweden
Ph. +46-08- 553 260 00
+46-08- 552 544 80

Kind Attn: Mr. Benjamin McDonald
Assistant General Counsel

Re: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent No. 206543.

Dear Sir,

We, **Lee Pharma Limited**, are a company incorporated under the Indian Companies Act, 1956 and have our principal place of business at Sy.No. 257 & 258/1,Door No.11-6/56-C,Opp. IDPL factory, Moosapet, Balanagar (Post), Hyderabad – 500 037, India.

We were incorporated in the year 1997, and since last more than 16 years, we have been involved in research and development, production, distribution, sales, marketing and export of pharmaceutical products, pharmaceutical formulations, intermediates and APIs. Presently our products are sold in India and exported to more than 48 countries worldwide and are known and appreciated for their quality and economical cost.

We are an ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP 100% EOU Certified company and one of the largest manufacturers of Bulk Drugs & Intermediates in India. We have three manufacturing units which are situated in Hyderabad and Vishakhapatnam, India.

We have established a State-of-Art Research and Development center and a dedicated and experienced team of senior scientists who are consistently and extensively involved in R & D activities and have developed many novel processes, compounds and intermediates. We are spending substantially high amount of money in R&D activities every year and have filed many

Corporate Office : Sy. No. 257& 258/1, Door No : 11-6/56, C-Block, Opp. IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad - 500037, A.P., INDIA Tel : 91-40-66170334 / 35 / 36, E-mail : info@leepharma.com http://www.leepharma.com Fax : 91-40-66170330
Factory : Survey No. 10/G-1, Gaddapotharam (Village), Jinnaram (Mandal), Medak (Dist) - 502319, Tel.: 91-8458-277250 Fax : 91-8458-277148.

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patent applications for the novel processes, intermediates and compounds which are invented and developed by us.

We have also received award for Excellence in Research And Development from The Federation of Andhra Pradesh Chambers of Commerce and Industry (FAPCCI). Our in-house R & D unit is recognized by Department of Scientific and Industrial Research (DSIR), Ministry of Science and Technology, Govt. of India.

In addition to the above, we are one of the biggest bulk drug manufacture and suppliers for a large number of pharmaceutical companies in India. We also have a network of strong marketing team with PAN India presence and grass root penetration in urban and rural Indian market.

In due course of time, through our dedicated R & D and Production teams, we have developed the technology, infrastructure and facilities for industrial scale preparation of the DPP4 inhibitor compound Saxagliptin. We have developed the capabilities to manufacture and sell this product both as API and in tablet form at a much lower price than the existing market price.

Currently Onglyza tablet is sold in India at the below prices-

ONGLYZA 2.5 mg	Rs. 532/- per strip of 14 tablets	Rs. 38/- per tablet
ONGLYZA 5 mg	Rs. 548/- per strip of 14 tablets	Rs. 39.15/- per tablet.

Whereas, with our infrastructure and expertise, we are in a position to offer the above dosage forms at a much lower price, without any compromise on the quality of the medicine. We also have the infrastructure and facilities to manufacture and sell the tablets combining Saxagliptin and Metformin at a very reasonable and affordable price.

IPO MUMBAI 29-06-2015 16:03

Lee Pharma Limited
AN ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP

In a country like India which has a population of about 1.3 Billion; according to one study/data there are about 65 Million individuals suffering from diabetes. This is further expected to increase to 101 million by the year 2030. The alarming trend is that now the Indian population is getting onset of this disease at a younger age. The shift of Type-II Diabetes to younger age groups and takeoff point of prevalence of diabetes occurring at the age 25 – 35 years in India causes huge burden on the patient and his family. In a country where majority of the population is poor and cannot afford costly medicines, the price of life saving medicines which are required to be taken on daily basis for the rest of patient's life, is very crucial.

We understand that the compound Saxagliptin is covered in India under Indian Patent No. 206543, granted on April 30, 2007, to M/S Bristol-Myers Squibb Company of USA for a Patent term of 20 years from 5th March 2001 and it should expire on 4th March 2021, unless it was lapsed/ revoked earlier on any grounds.

Whereas, we have noticed that through an Assignment Deed, the ownership rights in the Indian Patent No. 206543 have been transferred / assigned to you i.e. AstraZeneca AB of the address SE-151 85, Sodertalje, Sweden.

We identified that even after passing of 7 years from the date of grant of above Indian patent, still the Saxagliptin tablets (ONGLYZA) are not available to the general public at reasonably affordable price and thereby the reasonable requirements of the general public is not being met.

In view of the above backgrounds and with the objectives of providing these medicines (Saxagliptin and Saxagliptin + Metformin combination) to the general public of India at reasonably affordable price and to satisfy the reasonable requirements of the Indian public, we request you to grant us license for manufacture and sell this medicine in India both as API and tablet formulations of Saxagliptin 2.5 mg and Saxagliptin 5 mg as well as tablets of Saxagliptin + Metformin combination.

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Lee Pharma Limited
AN ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP

We will be glad to know your terms and requirements for grant of such license to us. We are ready to extend our full cooperation and support to reach an amicable understanding on the license terms which you may suggest.

Looking forward to hearing from you as soon as possible, preferably within one month of the date of this letter.

Yours sincerely,

A. Venkata Reddy
Managing Director
Lee Pharma Limited.

Copy to-

1. AstraZeneca AB
Avishkar' Post box No. 2483
Off Bellary Road
Hebbal, Bangalore-560 024
+91-80-6774 8000+91-80-23622015

2. Remfry & Sagar
Patent Agents for AstraZeneca AB
Remfry House
Millennium Plaza
Sector 27, Gurgaon- 122 009
NCR, India
Ph. 0124-6806100

} original copy sent

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ANAND AND ANAND

Mailing Address
B-41, NIZAMUDDIN EAST, NEW DELHI-110013 INDIA

Office Location
PLOT NO. 17A, SECTOR 16A, FILM CITY, NOIDA - 201301 (UP), INDIA

PHONES : 91-120-4059300 (100 Lines) FAX : 91-120-4243056 - 057; 91-120-2510020

email@anandandanand.com www.anandandanand.com

Courier/Registered AD/Email

7th November, 2014

Mr. A. Venkata Reddy
Managing Director
Lee Pharma Limited
Sy. No. 257 & 258/1, Door No. 11-6/56
C-Block, Opp. IDPL Factory, Moosapet (Village)
Balanagar (Post) Hyderabad-500 037 (A.P.)
Tel.: +918548277250
e-mail : info@leepharma.com

Sub : License request for manufacturing and selling SAXAGLIPTIN in India covered by Indian Patent No.206543

Dear Mr. Reddy,

We act on behalf of our client AstraZeneca AB, SE-151 85, Sodertalje, Sweden and have been instructed to address you as follows:

1. Our client is in receipt of your letter dated 31st October 2014. Our client was also in receipt of your letter dated 2nd May 2014 in which you have requested for a voluntary license for manufacturing and selling **SAXAGLIPTIN** in India.

2. Our client in an email dated 2nd June 2014 has responded to your letter dated 2nd May 2014. The same is attached as **Annexure A**. The email address to which this response was sent is provided in your letters of 2nd May 2014 and 31st October 2014.

Kindly consider the said email as a response to both your letters.

Yours sincerely,

for: **(Archana Shanker)**
Senior Partner
Anand and Anand

Encl: Annexure A

IPO MUMBAI

A Muraleedharan

From: Kramer, Sebastian [Sebastian.Kramer@astrazeneca.com]
Sent: Monday, June 02, 2014 8:58 PM
To: info@leepharma.com
Cc: McDonald, Benjamin
Subject: License request for manufacturing and selling SAXAGLIPTIN in India covered by Indian Patent No.206543
Attachments: letter from Lee Pharma.pdf

For the attention of A. Ventaka Reddy

Dear Mr Reddy,

I refer to your attached letter, in which you have requested for a voluntary license for manufacturing and selling **SAXAGLIPTIN** in India.

In order to enable us consider and assess your request, we would be grateful if you provide us with certain clarifications about your Company:

1. Please provide us details of the notable pharmaceutical products, pharmaceutical formulations, intermediates and APIs developed, produced, distributed, sold, marketed and exported by you;
2. Please state the notable countries and the cities and markets in India that you sell your products;
3. Please provide us with a copy of the certifications for your three manufacturing units located in Hyderabad and Visakhapatnam in India including the certificates for ISO 9001:2008, ISO 14001:2004, EU GMP and WHO GMP 100% EOU;
4. Please provide us with your field force strength;
5. Further, please provide us with the published patent applications and patents for the novel processes, intermediates and compounds invented and developed by your company;
6. Can you please also confirm the other class of DPP4 inhibitors that you are currently manufacturing, marketing and/or offering for sale?
7. Please provide us with proof of the awards received from FAPCCI and the DSIR, Ministry of Science and Technology, Government of India;
8. Please let us know if you have obtained any marketing approval or manufacturing license for SAXAGLIPTIN API or SAXAGLIPTIN tablets including SAXAGLIPTIN+METFORMIN from the Drug Controller General of India or any State Drug Regulatory Authority; and
9. Please let us know the price at which you propose to sell SAXAGLIPTIN in India and how have you arrived at the said price.

Since a request for a voluntary license is in the nature of a business negotiation, we reserve our right to seek additional information about your company.

While we await answers to the above questions, we strongly disagree with you that the SAXAGLIPTIN tablets sold by us under the brand name ONGLYZA are not available to the general public or that the reasonable requirements of the general public are not being met or that SAXAGLIPTIN is not available at a reasonably affordable price.

Notwithstanding the same, we look forward to receiving the information requested.

Yours sincerely,

Sebastian Kramer
Senior Counsel

AstraZeneca Global Litigation
Room 1S82
Mereside
Alderley Park

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Lee Pharma Limited
An ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP 100% EOU

May 02, 2014

M/S Astra Zeneca AB
SE-151 85, Södertälje
Sweden
Ph. +46-08- 553 260 00
+46-08- 552 544 80

Kind Attn: Mr. Benjamin McDonald
Assistant General Counsel

Re: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent No: 206543.

Dear Sir,

We, **Lee Pharma Limited**, are a company incorporated under the Indian Companies Act, 1956 and have our principal place of business at Sy.No. 257 & 258/1, Door No.11-6/56-C, Opp. IDPL factory, Moosapet, Balanagar (Post), Hyderabad – 500 037, India.

We were incorporated in the year 1997, and since last more than 16 years, we have been involved in research and development, production, distribution, sales, marketing and export of pharmaceutical products, pharmaceutical formulations, intermediates and APIs. Presently our products are sold in India and exported to more than 48 countries worldwide and are known and appreciated for their quality and economical cost.

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Lee Pharma Limited

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Lee Pharma Limited

We will be glad to know your terms and requirements for grant of such license to us. We are ready to extend our full cooperation and support to reach an amicable understanding on the license terms which you may suggest.

Looking forward to hearing from you as soon as possible, preferably within one month of the date of this letter.

Yours sincerely,

A. Venkata Reddy
Managing Director
Lee Pharma Limited

Copy to-

1. AstraZeneca AB
Avishkar' Post box No. 2483
Off Bellary Road
Hebbal, Bangalore-560 024
+91-80-6774 8000+91-80-23622015

2. Remfry & Sagar
Patent Agents for AstraZeneca AB
Remfry House
Millennium Plaza
Sector 27, Gurgaon- 122 009
NCR, India
Ph. 0124-6806100

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322

Lee Pharma Limited

AN ISO 9001:2008, ISO 14001:2004, EU GMP & WHO GMP
CIN : U24230TG1997PLC028095

November 22, 2014

To
Mr. Sebastian Kramer
Senior Counsel
AstraZeneca Global Litigation
Room 1S82, Mereside, Alderley Park
Cheshire, SK10 4TG
Ph. +44(0) 1625 515635

Re: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent No. 206543

Dear Mr. Kramer,

Thank you for your email dated June 02, 2014, asking us to provide certain clarifications about our company. Unfortunately, we could not receive your said email, probably due to some technical error, therefore, we sent our further letter on 31st October 2014 requesting your reply to our license request.

However, now a copy of your 2nd June email has been provided to us by your Indian counsel and we are therefore pleased to provide you all requested details as follow:

1. We manufacture and supply a large number of intermediates, APIs and pharmaceutical formulations. A comprehensive list of the products is enclosed as Annexure-A.

2. Our products are sold in about 56 countries worldwide either directly of through our channel partners. Similarly, we have a pan India presence and sell our products in all major Indian markets either directly or through our co-marketing partners. A list of countries is enclosed as Annexure-B.

3. Certification/approval details of our manufacturing units located in Hyderabad and Visakhapatnam, India are given in enclosed Annexure-C.

4. Through our direct and co-marketing partners, we have an efficient field force to market any product in Indian market across the country.

5. A complete list of our published patent applications for the novel processes, intermediates and compounds invented and developed by us is enclosed as Annexure-D.

Sy. No. 257 & 258/1, Door No : 11-6/56, C-Block, Opp: IDPL Factory, Moosapet, Balanagar (Post), Hyderabad - 500 037. T.S., INDIA
Tel : 91-40-66170334 / 66170335 / 66170336 / 23770338 / 23770339
E-mail : info@leepharma.com http://www.leepharma.com Fax : 91-40-66170330

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Lee Pharma Limited
AN ISO 9001:2008, ISO 14001: 2004, EU GMP & WHO GMP

6. Currently we are not manufacturing any DPP4 inhibitor except some advance intermediates of Saxagliptin and Linagliptin.

7. Copies of the awards received by us from FAPCCI and DSIR, Ministry of Science and Technology are enclosed as Annexure-E.

8. Till date we have not applied for any marketing approval or drug license for manufacturing SAXAGLIPTIN API or SAXAGLIPTIN tablets including SAXAGLIPTIN + METFORMIN but we are in a position to obtain the same in 8-12 weeks once we come to an understanding with you.

9. We propose to sell Saxagliptin 2.5 mg tablets to Indian patients at maximum retail price (MRP) of Rupees 20.00 per tablet.

We also propose to sell Saxagliptin 5 mg tablets to Indian patients at maximum retail price (MRP) of Rupees 22.00 per tablet.

In addition to the above, we can supply the bulk Saxagliptin API at a very reasonable and competitive price.

We are able to sell Saxagliptin at such a low price and pass on the cost benefits to Indian patients and to our customers due to our economical and industrially viable process.

We hope with the above details we were able to satisfy all your queries and your concerns thereof.

Looking forward to receiving your affirmative reply soon.

Yours sincerely,
For Lee Pharma Ltd.,

LEE PHARMA LIMITED HYDERABAD

A. Ventaka Reddy
Managing Director

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Annexure – A

LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Under campagin

	Products/ Therapeutic category	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
Antihypertensive			
1	Valsartan	In-House	Tech. Pack available
2	Olmesartan	In-House	Tech. Pack available
3	Azilsartan	In-House	Tech. Pack available
4	Telmisartan	In-House	Tech. Pack available
Antiosteoporosis			
5	Strontium Ranelate	In-House	Tech. Pack available
Antipsychotic			
6	Aripiprazole	In-House	Tech. Pack available
7	Levosulpiride	In-House	Tech. Pack available
Antidepressant			
8	Vilazodone HCl	In-House	Tech. Pack available
Anticonvulsant			
9	Lacosamide	In-House	Tech. Pack available
Antibacterial			
10	Prulifloxacin HCl	In-House	Tech. Pack available
Antispasmodic			
11	Trospium Chloride	In-House	Tech. Pack available
Antihistaminic			
12	Azelastine	In-House	Tech. Pack available

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LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Regular/Commercial

#	Therapeutic products	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
Hyper Lipidemic/ HMG- COA reductase			
1	Atorvastatin Calcium	IP	CTD compiled
		EP/USP	Technical Package available
2	Rosuvastatin Calcium	IP	CTD available as per IP
		ICH/ Ph-Eur	Technical Package available
Antihypertensive			
3	S- Amlodipine Besylate	IDL-CHINA	CTD compiled
4	S - Amlodipine Maleate	IDL-CHINA	CTD compiled
5	Enalaprilat	In-House	Tech. Pack available
6	Cilnidipine	In-House	Tech. Pack available
Antiplatetelet			
7	Clopidogrel Bisulfate Form I	USP	CTD compiled
8	Clopidogrel Bisulfate Form II	USP	Tech. Pack available
9	Prasugrel HCL	In-House	Tech. Pack available
Antiulcerative			
10	Omeprazole	EP	CEP available
11	Omeprazole Sodium	EP	Tech. Pack available
12	Omeprazole Magnesium	EP	CTD filed
		USP	Tech. Pack available
13	Esomeprazole Sodium	ICH	CTD compiled
14	Esomeprazole Magnesium Trihydrate	EP	CTD compiled
15	Esomeprazole Magnesium Dihydrate	ICH	CTD compiled
16	Lansoprazole	EP/USP	CEP available
17	DexLansoprazole	ICH	Tech. Pack available
18	Pantoprazole Sodium Sesquihydrate	EP	CEP Available
		USP	Tech. Pack available
19	Pantoprazole Magnesium Dihydrate	ICH	CTD compiled
20	Rabeprazole Sodium	In-House/Ph-Eur	CTD compiled
Anticonvulsant			
21	Pregabalin	ICH /Ph-Eur	CTD compiled
Antiosteoporosis			
22	Ibandronate Sodium	In-House/ USP	CTD compiled
23	Residronate Sodium	In-House/ USP	CTD compiled
Antipsychotic			
24	Olanzapine Form I	In-house/EP/USP	CTD Filed
25	Olanzapine Form II	EP	Tech. Pack available
26	Olanzapine Form V	USP	CTD compiled

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LEE PHARMA LIMITED

ACTIVE PHARMACEUTICAL INGREDIENTS - Regular/Commercial

#	Therapeutic products	Pharmacopeial grade IP/EP/BP/USP/JP/In-house/ICH	DMF Status
27	Asenapine Maleate	In-House	CTD compiled
28	Lurasidone Hydrochloride	In-House	Tech. Pack available
Antifungal			
29	Itraconazole	EP	CEP available
30	Voriconazole	EP	CEP Filed
31	Terconazole	In-House	CTD compiled
Antihistaminic			
32	Cetrizine dihydrochloride	EP	CTD is under compilation
33	Levocetrizine Dihydrochloride	IP	CTD compiled
34	Montelukast Sodium	IP/EP/USP	Tech. Pack available
Antidepressant			
35	Duloxetine HCl	EP	CTD is under compilation
36	Sertraline HCl	EP	CTD compiled
37	Sertraline HCl Form I	EP	Tech. Pack available
38	Sertraline HCl Form II	EP	CTD Filed
39	Venlafaxine HCl	EP	CTD Filed
40	DesVenlafaxine Succinate	In-House	Tech. Pack available
Antibacterial			
41	Linezolid Form II	In-House	CTD is under compilation
42	Moxifloxacin HCl	EP/USP	CTD is under compilation
Overactive Bladder			
43	Fesoterodine Fumarate	In-House	Tech. Pack available
Benign Prostatic Hypertrophy			
44	Tamsulosin HCl	EP	CTD compiled
Anti Coagulant			
45	Dabigatran Etexilate mesylate	In-House	Tech. Pack available
Premature Ejaculation			
46	Dapoxetine Hcl	In-House	Tech. Pack available
Anti-Inflammatory (NSAID)			
47	Etoricoxib	In-House	Tech. Pack available
Anti-gout			
48	Febuxostat	In-House	Tech. Pack available

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LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
1	2-chloromethyl-3-methyl-4- (2,2,2-trifluoroethoxy) pyridine hydrochloride (Lansoprazole chloro compound)	Lansoprazole	127337-60-4
2	2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridine-2-yl] methyl]thio]-1H-benzimidazole (Lansoprazole Sulphide compound)	Lansoprazole	103577-40-8
3	2-(Chloromethyl)-3,4-dimethoxy pyridine hydrochloride (Pantoprazole Chloro Compound)	Pantoprazole sodium	72830-09-2
4	5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl] thio]-1H-benzimidazole (Pantoprazole Sulphide compound)	Pantoprazole sodium	102625-64-9
5	2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] thio]-1H-benzimidazole (Rabeprazole Sulphide compound)	Rabeprazole	117977-21-6
6	Cis-[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan -4-yl] methanol-p-Toluenesulfonate	Terconazole Itraconazole	103661-14-9
7	4-(4-Hydroxy phenyl)-1-(1-methylethyl)piperazine	Terconazole	67914-97-0
8	(R*,S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidine-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol	Voriconazole	188416-29-7
9	2-(2,4-difluorophenyl)-3-(4-chloro-5-fluoro pyrimidine-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol hydrochloride	Voriconazole	188416-35-5
10	(S)-3-(dimethylamino)-1-(thiophen-2-yl) propan-1-ol-2-hydroxy-2-phenylacetate	Duloxetine Hydrochloride	287737-72-8
11	2-(2-Nitro anilino)-5-methyl thiophene-3-carbonitrile	Olanzapine	138564-59-7
12	4-amino-2-methyl-10H-thieno [2,3-b] [1,5] benzodiazepine hydrochloride	Olanzapine	138564-60-0
13	7-(4-bromo butoxy)-3,4-dihydro carbostyril	Aripiprazole	29722-34-5
14	(R)-5-(2-aminopropyl)-2-methoxy-benzenesulfonamide	Tamsulosin HCl	112101-81-2
15	1-(2-bromoethoxy)-2-ethoxy-benzene	Tamsulosin HCl	3259-03-8
16	(R)-5-bromo-3-[(1-methyl-2-pyrrolidinyl)methyl]-1H-indole	Eletriptan	143322-57-0
17	2-Bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone	Prasugrel	204205-33-4
18	Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester	Fesoterodine Fumerate	156755-35-0
19	(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine	Fesoterodine Fumerate	207679-81-0
20	N-[3-amino-4-(methylamino)benzoyl]-N-2-pyridinyl-, ethyl ester	Dabigatran	212322-56-0
21	2-(n-Butyl)-3-(4-hydroxybenzoyl)-5-nitrobenzofuran	Dronedarone	141645-16-1
22	Methyl 2-[1-[[(benzyloxy)carbonyl]amino]-1-methylethyl]-5,6-dihydroxypyrimidine-4-carboxylate	Raltegravir	519032-08-7
23	Methyl 2-[1-[[(benzyloxy)carbonyl]amino]-1-methylethyl]-1-Methyl-5-Hydroxy-6-Oxo-1,6-dihydroxypyrimidine-4-carboxylate	Raltegravir	888504-27-6
24	Benzyl [1-[4-[[(4-Fluorobenzyl]amino]carbonyl]-5-Hydroxy-1-Methyl-6-Oxo-1,6-Dihydropyrimidine-2-yl]-1-Methylethyl]Carbamate	Raltegravir	518048-02-7
25	5-Methyl-1,3,4-Oxadiazole-2-Carboxylic Acid Potassium Salt	Raltegravir	888504-28-7
26	(1S,3S,5S)-3-(Aminocarbonyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester	Saxagliptan	361440-67-7

LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
27	(1S,3S,5S)-2-Azabicyclo[3.1.0]hexane-3-carboxamide	Saxagliptan	361440-68-8
28	(1S,3S,5S)-2-Azabicyclo[3.1.0]hexane-3-carboxamide, 2,2,2-trifluoroacetate (1:1)	Saxagliptan	361440-69-9
29	(aS)-a-[[(1,1-dimethylethoxy)carbonyl]amino]-3-hydroxytricyclo[3.3.1.13,7]decane-1-acetic acid	Saxagliptan	361442-00-4
30	3-(1-Piperazinyl)-1,2-Benzisothiazole	Lurasidone	87691-87-0
31	(3aR,4S,7R,7aS) 4,7-Methano-1H-isoindole-1,3(2H)-dione	Lurasidone	14805-29-9
32	(R,R) Cyclohexane Dicarboxylic Acid	Lurasidone	46022-05-3
33	(3aR, 7aR)-Hexahydroisobenzofuran-1,3-Dione	Lurasidone	71749-03-6
34	2,3,4,5-Tetrahydro-3-(Trifluoroacetyl)-1,5-Methano-1H-3-Benzazepine	Varenicline	230615-51-7
35	2,3,4,5-Tetrahydro-1,5-Methano-1H-3-Benzazepine Hydrochloride	Varenicline	230615-52-8
36	8-Bromo-7-(But-2-ynyl)-3-Methyl-1H-Purine-2,6(3H,7H)-Dione,	Linagliptin	666816-98-4
37	3-(R)-Piperdinyl Pthalimide Hydrochloride	Linagliptin	886588-61-0
38	(R)-Tert-Butyl piperdin-3-yl Carbamate	Linagliptin	309956-78-3
39	1-(Isobutyloxy)ethyl-4-Nitrophenyl Carbonate	Gabapentin	NA
40	(1R,2S,5S)-6,6-Dimethyl-3-Aza-Bicyclo[3.1.0]Hexane-2-Carboxylic Acid Methyl Ester Hydrochloride	Boceprevir	565456-77-1
41	Beta-Amino-Alpha-Hydroxycyclobutanebutanamide Hydrochloride	Boceprevir	394735-23-0
42	N-[(1,1-dimethylethoxy)carbonyl]-3-methyl-L-valine	Boceprevir	62965-35-9
43	1-[N-(2,6-Dimethylphenyl)carbomylmethyl]piperazine	Ranolazine	5294-61-1
44	(2-methoxyphenoxy)-2,3-Epoxypropane	Ranolazine	2210-74-4
45	3-(4-chlorobutyl)-1H-indole-5-carbonitrile	Vilazodone	143612-79-7
46	Ethyl 5-(piperazin-1-yl)-1-benzofuran-2-carboxylate	Vilazodone	163521-20-8
47	4-Oxo-1,4-Dihydroquinoline-3-Carboxylic Acid	Ivacaftor	13721-01-2
48	5-Amino-2,4-Di-Tert-Butylphenyl methyl carbonate	Ivacaftor	1182822-31-6
49	2-Chloromalonaldehyde	Etoricoxib	36437-19-1
50	1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl] Ethanone	Etoricoxib	221615-75-4
51	4-amino-1- ((2R,3R,4R,5R)-3- fluoro-4-hydroxy-5- (hydroxymethyl)-3-methyltetrahydrofuran- 2-yl)pyrimidin-2(1H)-one	Sofusbuvir	817204-33-4
52	1-(4- iodophenyl) – piperidine -2- one	Apixaban	385425-15-0
53	Chloro (4- methoxyphenyl) hydrazono) acetic acid ethyl ester	Apixaban	27143-07-3
54	2- Piperiodone	Apixaban	675-20-7
55	(S,S)-2,8-Diazabicyclo[4,3,0] nonane	Moxifloxacin Hydrochloride	151213-40-0
56	1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid ethyl ester	Moxifloxacin Hydrochloride	112811-71-9

LEE PHARMA LIMITED
INTERMEDIATE CHEMICALS

Sl. No.	Intermediate Name	Product Name	CAS Number
57	(2-[2-[3(S)-[3-[(1E)-2-(7-chloroqunolin-2-yl)phenyl]-3-hydroxypropyl]phenyl-2-propanol)	Montelukast sodium	142569-70-8
58	(1-(Mercaptomethyl) cyclopropane acetic acid)	Montelukast sodium	162515-68-6

LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

ENTERIC COATED / DELAYED RELEASE PELLETS	DMF STATUS
Omeprazole	DMF Filed
Lansoprazole	DMF Filed
Esomeprazole Magnesium Trihydrate	DMF Filed
Esomeprazole Magnesium Dihydrate	T/P available
Rabeprazole Sodium	DMF Filed
Pantoprazole Sodium	DMF Compiled
Diclofenac Sodium	T/P available
Diclofenac Potassium	T/P available
Mebeverine Hcl	DMF Compiled
Duloxetine HCl	T/P available
Aspirin	DMF Filed
Omeprazole + Domperidone	T/P available
Lansoprazole + Domperidone	T/P available
Pantoprazole + Domperidone	T/P available
Rabeprazole + Domperidone	T/P available
Clopidogrel + Aspirin	T/P available
Prasugrel + Aspirin	T/P available
Dexlansoprazole	T/P available
IMMEDIATE RELEASE PELLETS	**DMF STATUS**
Itraconazole	DMF Filed
Orlistat	DMF Filed
Domperidone	T/P available
Folic Acid	T/P available
Levocetirizine Di HCl	T/P available
Cetirizine HCl	T/P available
Atorvastatin	T/P available
Ferrous Ascorbate	T/P available
Mebeverine Hcl	T/P available
Fenofibrate	DMF Compiled
Secnidazole	T/P available
Prasugrel	T/P available
Rosuvastatin Calcium	T/P available
SUSTAINED RELEASE PELLETS	**DMF STATUS**
Venlafaxine Hcl	DMF Compiled
Diltiazem Hcl	T/P available
Indomethacin	T/P available
Itopride	T/P available
Tamsulosin Hcl	DMF Compiled
Mebeverine Hcl	DMF Compiled

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LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

SUSTAINED RELEASE PELLETS	DMF STATUS
Metoprolol Succinate	CTD compiled
Propranolol	T/P available
Pseudophedrine	T/P available
Diclofenac Sodium	T/P available
Diclofenac Potassium	T/P available
Domperidone	DMF Compiled
Fenofibrate	T/P available
Ambroxol	T/P available
Nifedipine	T/P available
Trimetazidine	T/P available
Theophylline	T/P available
Tizanidine	T/P available
Aceclofenac	T/P available
Cinitapride	T/P available
Desvenlafaxine	T/P available

SUSTAINED RELEASE PELLETS	DMF STATUS
Isosorbide Dinitrate	T/P available
Isosorbide Mononitrite	T/P available
Isoxsuprine hcl	T/P available
Ferrous Fumarate	T/P available
Ascorbic acid	T/P available
Dried Ferrous Sulphate , Zinc Sulphate monohydrate & Folic Acid	T/P available
Atorvastatin + Fenofibrate	T/P available
Galanthamin Hydrobromide	T/P available
Cyclobenzaprine HCl	T/P available
Minocycline HCl	T/P available
Trospium Chloride	T/P available
Nicardipine HCl	DMF Compiled
Phenylephrine HCl	T/P available
Fesoterodine fumarate	T/P available
Caffeine	T/P available
Pseudoephidrine + Loratidine	T/P available
Dipyridamole	T/P available
Chloropheniramine Maleate	T/P available
Carvedilol Phosphate	T/P available
Mesalamine	T/P available

MULTIPLE UNIT PELLETS (MUPS)	DMF STATUS
Omeprazole	T/P available
Lansoprazole	T/P available
Esomeprazole Mg. Trihydrate	T/P available
Esomeprazole Mg. Dihydrate	T/P available

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LEE PHARMA LIMITED

PELLETS AND GRANULES

MODIFIED RELEASE DOSAGE FORMS

TASTE - MASKED GRANULES FOR SUSPENSION	DMF STATUS
Omeprazole	T/P available
Esomeprazole Magnesium	T/P available
Azithromycin	T/P available
Clarithromycin	T/P available
Roxithromycin	T/P available
Ciprofloxacin	T/P available
Ibuprofen	T/P available
DIRECTLY COMPRESSIBLE GRANULES	**DMF STATUS**
Atorvastatin	T/P available
Simvastatin	T/P available
Atorvastatin + Fenofibrate	T/P available
Simvastatin + Fenofibrate	T/P available
Ciprofloxacin	T/P available
Atorvastatin+ Ezetimibe	T/P available
Clopidogrel + Aspirin	T/P available

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Annexure – B

List or countries			
1	Algeria	29	Moldova
2	Argentina	30	Morocco
3	Bangladesh	31	Netherlands
4	Belarus	32	Pakistan
5	Brazil	33	Paraguay
6	Bulgaria	34	Peru
7	Chile	35	Poland
8	Canada	36	Portugal
9	China	37	Romania
10	Colombia	38	Russia
11	Croatia	39	Saudi Arabia
12	Cyprus	40	Spain
13	Denmark	41	Sudan
14	Egypt	42	Sweden
15	Ethiopia	43	Switzerland
16	Greece	44	Singapore
17	Germany	45	UK
18	Hong Kong	46	Taiwan
19	Indonesia	47	Thailand
20	Iran	48	Tunisia
21	Israel	49	Turkey
22	Italy	50	Ukraine
23	Ireland	51	UnitedArabEmirates
24	Jordan	52	Uruguay
25	Korea	53	USA
26	Lebanon	54	Venezuela
27	Mexico	55	Vietnam
28	Malaysia	56	Yemen
29	Moldova		

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Annexure – C

LÆGEMIDDELSTYRELSEN

DANISH MEDICINES AGENCY

Certificate No. DK API-H 00022212

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC as amended.

The competent authority of *Denmark* confirms the following:

The manufacturer Lee Pharma Limited

Site address Survey No. 10/G-1
Gaddapotharam Village
Jinnaram Mandal
502319
Medak, Andhra Prad.
India

is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: *(Consolidated) Medicinal Products Act, 2005, as amended.*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2012/02/09, it is considered that it complies with the Good Manufacturing Practice requirements referred to in the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted.
The authenticity of this certificate may be verified with the issuing authority.

Axel Heides Gade 1
DK-2300 København S
Tel. +45 4488 9595 / Fax +45 4488 9195
www.laegemiddelstyrelsen.dk / dkma@dkma.dk

Printed on: 21-05-2012
Ref. No. / knb.
EMEA/INS/GMP/313556/2006 / MRA

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LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Certificate No. DK API-H 00022212

Part 2

Manufacture of active substance. Names of substances subject to inspection:
Omeprazole, Lansoprazole and Pantoprazole Sodium Sesquihydrate.

Any restrictions or clarifying remarks related to the scope of this certificate:
None
Date: 2012/05/11

Name and signature of the authorised person
of the competent authority of Denmark:

.....
Knud Ryhl

The Danish Medicines Agency

E-mail: dkma@dkma.dk
Fax: dkma@dkma.dk

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GOVERNMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION
** ** **

Office of the Designated Officer &.
Deputy Director,
Drugs Control Administration,
Vengalraonagar,
Hyderabad – 500 038.

L.Dis.No.4484/A3/2014 Dated 27-10-2014.

G.M.P. CERTIFICATE

This is to certify that **M/s. LEE PHARMA LIMITED**, situated at Sy.No.10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District is holding Drug Manufacturing Licence in Form – 25 bearing No. **35/MD/AP/2000/B/CC** dated 06.06.2000, valid upto 13.09.2015 for manufacture for sale or distribution of the drugs approved to them by this department. The firm is subjected to periodical inspection by this Department.

The firm is following **GOOD MANUFACTURING PRACTICES** as stipulated under the provisions of **SCHEDULE 'M'** of Drugs and Cosmetics Rules, 1945.

The firm should, however carryout self-inspection from time to time to ensure that the requirements of Good Manufacturing Practices are complies with.

This certificate is issued as requested by the firm for registering the drugs to various countries.

This certificate is valid for one year from the date of issue.

27/10/14

DEPUTY DIRECTOR & CERTIFYING AUTHORITY
DRUGS CONTROL ADMINISTRATION

Deputy Director (Enforcement) Drugs Control Administration Hyderabad Government of Telangana Designated Officer for Telangana

To

M/s. LEE PHARMA LIMITED,
Sy.No.10/G-1, Gaddapotharam Village,
Jinnaram Mandal, Medak District.

IPO MUMBAI 29-06-2015 16:03

Certificate of Registration

nqa.

This is to certify that the Quality Management System of

Lee Pharma Limited
Office: Sy. No. 257 & 258/1, Door No. 11-6/56-C, Opp. IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad - 500 037, Andhra Pradesh, India
Factory: 10/G-1, Gaddapotharam Village, Jinnaram Mandel, Medak District - 502 319, Andhra Pradesh, India

applicable to

Manufacturing, supply and sale of intermediate chemicals and active pharmaceuticals ingredients

has been assessed and registered by NQA against the provisions of

BS EN ISO 9001 : 2008

This registration is subject to the company maintaining a quality management system, to the above standard, which will be monitored by NQA.

Certificate No:	18461
Date:	23 September 2004
Reissued:	28 August 2013
Valid Until:	28 August 2016
EAC Code:	13

Certification Director

UKAS QUALITY MANAGEMENT 015

The use of the UKAS Accreditation Mark indicates accreditation in respect of those activities covered by the accreditation certificate number 015 held by NQA.
NQA is a trading division of Ascentiva Group Ltd, Registration No. 02513162. Registered Office: Warwick House, Houghton Hall Park, Houghton Regis, Dunstable, Bedfordshire, LU5 5ZX.
This certificate is the property of NQA and must be returned on request.

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Certificate of Registration

nqa.

This is to certify that the Environmental Management System of

Lee Pharma Limited
Office: Sy No. 257 & 258/1, Door No: 11-6/56-C, Opp: IDPL Factory, Moosapet (Village), Balanagar (Post), Hyderabad – 500 037, India
Factory: 10/G-1, Gaddapotharam Village, Jinnaram Mandel, Medak District – 502 319, A.P, India

applicable to

Manufacture, testing, packaging and sale of intermediate chemicals and active pharmaceutical ingredients

has been assessed and registered by NQA against the provisions of

BS EN ISO 14001 : 2004

This registration is subject to the company maintaining an environmental management system, to the above standard, which will be monitored by NQA.

Certificate No:	E 3326
Date:	14 September 2009
Reissued:	30 August 2012
Valid Until:	30 August 2015

Certification Director

UKAS ENVIRONMENTAL MANAGEMENT
015

The use of the UKAS Accreditation Mark indicates accreditation in respect of those activities covered by the accreditation certificate number 015 held by NQA.
NQA is a trading division of Ascertiva Group Ltd, Registration No. 02513162. Registered Office: Warwick House, Houghton Hall Park, Houghton Regis, Dunstable, Bedfordshire, LU5 5ZX.
This certificate is the property of NQA and must be returned on request.

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GOVERNMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION
** ** **

L.Dis.No.175/A3/2014. Dated 10 - 10 - 2014.

From

R. UDAY BHASKAR,
Designated Officer(I/c) & Assistant Director,
Licensing Authority & Controlling Authority,
Drugs Control Administration,
Vengalraonagar,
Hyderabad.

To

M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1,
Gaddapotharam Village,
Jinnaram Mandal,
Medak District,
Telangana, INDIA.

Sirs,

Sub: Drugs and Cosmetics Act, 1940 and Rules made thereunder – Issue of World Health Organization Good Manufacturing Practice Certificate – Regarding.

Ref: 1. Your application dated 04.06.2014.
2. Joint Inspection Report dated 23.09.2014 & 24.09.2014.

@@@

I forward herewith **WORLD HEALTH ORGANIZATION GOOD MANUFACTURING PRACTICE CERTIFICATE** for the products recommended by the Joint Inspection Team consisting of officers of Central Drugs Standard Control Organization and officer from Drugs Control Administration, Telangana for **Export** Purpose.

This Certificate is valid for a period of **Two** years from the date of issue.

Yours faithfully,

10/10/2014

DESIGNATED OFFICER(I/c) & ASSISTANT DIRECTOR
LICENSING AUTHORITY & CONTROLLING AUTHORITY
DRUGS CONTROL ADMINISTRATION

Deputy Director (Enforcement) ★ Drugs Control Administration ★ HYDERABAD ★ Government of Telangana ★ Designated Officer for Telangana

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GOVERNAMENT OF TELANGANA
DRUGS CONTROL ADMINISTRATION
** ** **

Office of the Designated Officer &
Deputy Director,
Drugs and Control Administration,
Vengalraonagar, Hyderabad – 500 038.

L.Dis.No.175/A3/2014 Dated 10-10-2014.

LIST OF PRODUCTS APPROVED UNDER WHO GMP CERTIFICATION SCHEME FOR EXPORT PURPOSE

1.	OMEPRAZOLE	USP/BP
2.	ITRACONAZOLE	BP
3.	LANSOPRAZOLE	USP
4.	OLANZAPINE	IHS
5.	ESOMEPRAZOLE MAGNESIUM TRIHYDRATE	Ph.Eur.
6.	SERTRALINE HYDROCHLORIDE	Ph.Eur.
7.	RABEPRAZOLE SODIUM	IH
8.	ENALAPRIL MALEATE	USP
9.	CLOPIDOGREL BISULPHATE	USP
10.	PANTOPRAZOLE SODIUM	USP
11.	RESIDRONATE SODIUM	IH
12.	OMEPRAZOLE MAGNESIUM	Ph.Eur.
13.	PREGABALIN	IH
14.	AMLODIPINE BESYLATE	BP/Ph.Eur.
15.	VORICONAZOLE	IHS
16.	ROSUVASTATIN CALCIUM	IH
17.	MOXIFLOXACIN HYDROCHLORIDE	BP/Ph.Eur.
18.	DULOXETIN HYDROCHLORIDE	IH
19.	TAMSULOSIN HYDROCHLORIDE	IP/IH
20.	VENLAFAXIN HYDROCHLORIDE	Ph.Eur.
21.	MONTELUKAST SODIUM	IP/Ph.Eur.
22.	ATORVASTATIN CALCIUM	IP/USP
23.	DESVENLAFAXINE SUCCINATE	IH
24.	ESOMEPRAZOLE SODIUM	IH

Manufacturer : M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1,
Gaddapotharam Village,
Jinnaram Mandal, Medak District,
Telangana, INDIA.

When applicable : Placing the products on the market as detailed above.

Deputy Director (Enforcement) ★ Designated Officer for Telangana ★ Drugs Control Administration HYDERABAD Government of Telangana

10/10/2014

IPO MUMBAI 29-06-2015 16:03

L.Dis.No.175/A3/2014:

WHO GMP CERTIFICATE Issued to M/s. LEE PHARMA LIMITED, Sy.No. 10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District, Telangana, INDIA

** ** **

It is certified that these products had been authorized to be placed on the market for use in the country and exporting countries.

Drug Licence No. : **35/MD/AP/2000/B/CC**, dated 06.06.2000, in Form – 25.

The Unit of M/s. LEE PHARMA LIMITED, Sy.No. 10/G-1, Gaddapotharam Village, Jinnaram Mandal, Medak District, Telangana, INDIA was inspected by Mrs. P. Indira, Drugs Inspector, O/o the Deputy Drugs Controller(India), CDSCO, Zonal Office, Hyderabad and Sri. K. Anil Kumar, Drugs Inspector, Drugs Control Administration, Hyderabad on 23.09.2014 and 24.09.2014.

The manufacturer conforms to requirement for **Good Manufacturing Practices** in the manufacturing and quality control (As recommended by the **World Health Organization**) in respect of the products mentioned above (**TWENTY FOUR** in number) for Export in the international market.

This certificate is valid for a period of **Two** years from the date of issue.

Deputy Director (Enforcement) ★ Designated Officer for Telangana ★ Drugs Control Administration HYDERABAD Government of Telangana

10/10/2014

DESIGNATED OFFICER(I/c) & ASSISTANT DIRECTOR
LICENSING AUTHORITY & CONTROLLING AUTHORITY
DRUGS CONTROL ADMINISTRATION

To
M/s. LEE PHARMA LIMITED,
Sy.No. 10/G-1, Gaddapotharam Village,
Jinnaram Mandal, Medak District,
Telangana, INDIA.

IPO MUMBAI 29-06-2015 16:03

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SALUD
SECRETARÍA DE SALUD

Cofepris
Comisión Federal para la Protección contra Riesgos Sanitarios

ESTADOS UNIDOS MEXICANOS
COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS
COMISIÓN DE AUTORIZACIÓN SANITARA
SUBDIRECCIÓN EJECUTIVA DE LICENCIAS SANITARIAS

"2013, Año de la Lealtad Institucional y Centenario del Ejercito Mexicano"

CERTIFICADO No. 133300CI110227

México, D.F. a 10 de Septiembre de 2013

LEE PHARMA LIMITED
Por conducto de su representante legal o apoderado legal
o quien legalmente represente sus derechos.
Plot No. V, Phase II, Vsez, Duvvada,
Sabbavaram (Mandal) Visakhapatnam District,
Andhra Pradesh, India.
PRESENTE

Con fundamento en los artículos 4° párrafo cuarto, 8 y 14 de la Constitución Política de los Estados Unidos Mexicanos; 39 de la Ley Orgánica de la Administración Pública Federal; 1; 3 y 16 fracción X de la Ley Federal del Procedimiento Administrativo; 3 fracciones XXIV y XXVI, 4 fracción III, 17 bis fracción V, 194, 197 287, 388, 389 fracción V, 391 bis y 392 de la Ley General de Salud; 1 y 2 inciso c fracciones X del Reglamento Interior de la Secretaría de Salud; 1, 3 fracción I inciso b y VI, 4 fracción II inciso c y 14 fracción IX del Reglamento de la Comisión Federal para la Protección contra Riesgos Sanitarios; 1, 167 fracción VI, 170 fracción II, 190 bis 1 fracción VI, 190 bis 2 fracción III, 190 bis 3 fracción VI, 190 bis 4 fracción II, 208 del Reglamento de Insumos para la Salud modificado el 02 de enero de 2008; vigésimo primero del Acuerdo por el que se modifica el diverso por el que se delegan las facultades que se señalan, en los órganos administrativos que en el mismo se indican de la Comisión Federal para la Protección contra Riesgos Sanitarios, Publicado en el Diario Oficial de la Federación el 7 de abril de 2010 y el 23 de marzo de 2012; así como los relativos y aplicables del Acuerdo por el que se modifica el diverso por el que se dan a conocer los trámites inscritos en el Registro Federal de Trámites Empresariales que aplica la Secretaría de Salud y se establecen diversas medidas de mejora regulatoria y por el que se dan a conocer los formatos para la realización de trámites que aplica la Secretaría de Salud, a través de la Comisión Federal para la Protección Contra Riesgos Sanitarios, publicado el 23 de octubre de 2012 en el Diario Oficial de la Federación; y por medio del presente se hace constar que la **empresa citada al rubro**, clasificada como Fabrica o Laboratorio de Materias Primas para la Elaboración de Medicamentos o Productos Biológicos para uso Humano, cuenta con Licencia Sanitaria No. 33/VP/AP/2010/F/G, cumple con las Buenas Prácticas de Fabricación exigidas por las Autoridades Sanitarias en México, conforme a la Legislación Sanitaria Vigente en la materia y sus instalaciones están sujetas a verificación por parte de esta Comisión Federal, por lo que está autorizada para fabricar los siguientes productos obtenidos por síntesis química, desde el principio activo hasta su presentación comercial en pellets:

- **Venlafaxina HCl SR Pellets 33% y Tamsulosina HCl SR Pellets 0.2%, en presentación de cuñetes de plástico de 25.00 Kg.**

Se expide el presente Certificado a petición del interesado para los fines legales a que haya lugar, el cual vence el día 09 de [illegible] 2016, pero al modificar las condiciones en que fue otorgado o presentar desviaciones el Certificado queda sin efecto.

SUBDIRECTOR EJECUTIVO DE LICENCIAS SANITARIAS

MARCOS LAUREANO SOLIS LEYVA

SECRETARÍA DE SALUD
COMISION FEDERAL DE PROTECCION CONTRA RIESGOS SANITARIOS
SUBDIRECCION EJECUTIVA DE LICENCIAS SANITARIAS

En el ejercicio de la facultad delegada en el artículo Vigésimo Primero del Acuerdo por el que se modifica el diverso por el que se delegan las facultades que se señalan, en los órganos administrativos que en el mismo se indican de la Comisión Federal para la Protección contra Riesgos Sanitarios. Publicado en el Diario Oficial de la Federación el 7 de abril de 2010 y el 23 de marzo de 2012.

c.c.p. Expediente de la Comisión de Autorización Sanitaria, 1° Piso.

IVCB/NEST 09.09.13 SLS/04/0384/2013 CBPF FIN TD

Oklahoma No. 14, Col. Nápoles, Del. Benito Juárez, D.F., C.P. 03810
Tel. 5080-5200 (Ext. 1366) 01 800 033 50 50 www.cofepris.gob.mx

COF 002037

Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subdirección Ejecutiva de Licencias Sanitarias Comisión de Autorización Sanitaria Subd

CAS-SELS

IPO MUMBAI 29-06-2015 16:03

LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Certificate No. DK API-H 00022312

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC as amended.

The competent authority of *Denmark* confirms the following:

The manufacturer Lee Pharma Limited, Plot No. V, Phase-II

Site address Vsez, Duvvada
530049
Vishakapatnam, AP
India

is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: *(Consolidated) Medicinal Products Act, 2005, as amended.*

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2012/02/03, it is considered that it complies with the Good Manufacturing Practice requirements referred to in the principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted.
The authenticity of this certificate may be verified with the issuing authority.

Axel Heides Gade 1
DK-2300 København S
Tel. +45 4488 9595 / Fax +45 4488 9195
www.laegemiddelstyrelsen.dk / dkma@dkma.dk

Printed on: 21-05-2012
Ref. No. / KNB.
EMEA/INS/GMP/313556/2008 / MRA

IPO MUMBAI 29 MAY 2012

The certificate may not be reproduced, except in its complete form, without a written consent of the Danish Medicine Agency

LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Certificate No. DK API-H 00022312

Part 2

Manufacture of active substance. Names of substances subject to inspection:
Modified released dosage form (Pellets) of Omeprazole, Lansoprazole and Itraconazole

Any restrictions or clarifying remarks related to the scope of this certificate:
None
Date: 2012/05/11

Name and signature of the authorised person
of the competent authority of Denmark:

.....
Knud Ryhl

The Danish Medicines Agency

E-mail: dkma@dkma.dk
Fax: dkma@dkma.dk

IPO MUMBAI 29 MAR 2013 10:00

The certificate may not be reproduced, except in its complete form, without a written consent of the Danish Medicine Agency

GOVERNMENT OF ANDHRAPRADESH
DRUGS CONTROL ADMINISTRATION

Office of the Deputy Director,
Drugs Control Administration,
Visakhapatnam Region,
Visakhapatnam -530 003.

File.No.1548/DD/DCA/VSP/2014 Dated: 12-02-2014

G.M.P. CERTIFICATE

This is to certify that M/s LEE PHARMA LIMITED, Plot No.V, Phase-II, VSEZ, Duvvada, Sabbavaram (M), Visakhapatnam District is holding license in Form-25 bearing No. **33/VP/AP/2010/F/G**, Dated. 15-07-2010, Valid up to 14-07-2015 for manufacture, for sale or distribution of drugs approved by this Department. The firm is subjected to periodical Inspection by this Department.

The firm is following **GOOD MANUFACTURING PRACTICES** as stipulated under the provisions of Schedule 'M' of Drug and Cosmetics Rules, 1945.

The firm should however carry out self inspection from time to time to ensure that the requirements of Good Manufacturing Practices are complied with.

The Certificate is valid for One Year from the date of Issue.

O/o Dy. Director DCA Govt. of A.P VISAKHAPATNAM

(L. PRAMOD REDDY)
DEPUTY DIRECTOR & CERTIFYING AUTHORITY
DRUGS CONTROL ADMINISTRATION
VISAKHAPATNAM REGION
DEPUTY DIRECTOR
Drugs Control Administration
Visakhapatnam

To
M/s LEE PHARMA LIMITED,
Plot No.V, Phase-II, VSEZ,
Duvvada, Sabbavaram (M),
Visakhapatnam District, Andhra Pradesh
India.

Copy to: The Joint Director –II, Drugs Control Administration, Hyderabad for favor of information.

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GOVERNMENT OF ANDHRA PRADESH
DRUGS CONTROL ADMINISTRATION

L.Dis.No.12836/M1A/Mfg/2012 Dated 21-09-2012

From

R.V.S.R.B.Sarma,
Joint Director & Licensing Authority,
O/o.the Director General,
Drugs and Copyrights,
Drugs Control Administration,
Vengalraonagar, Hyderabad – 500 038.

To

M/s.Lee Pharma Limited,
Plot No.V, Phase-II, VSEZ,
Duvvada,
Sabbavaram (M)
Visakhapatnam District,
Andhra Pradesh, India.

Sir,

Sub: Drugs and Cosmetics Act, 1940 and rules made thereunder – Issue of World Health Organisation Good Manufacturing Practice Certificate – Regarding.

Ref:
1. Your application dt: 02-05-2012 & 22-08-2012.
2. Joint inspection, dt: 06-07-2012.
3. Lr.Rc.No.302/DD/VSP/2012 dt: 07-09-2012 of the Deputy Director, DCA, Visakhapatnam District.
4. Lr.Rc.No.144/AD/VSP/2012 dt: 27-08-2012 of the Assistant Director, DCA, Visakhapatnam District.

I forward herewith **WORLD HEALTH ORGANISATION GOOD MANUFACTURING PRACTICE CERTIFICATE** for the products recommended by the Joint Inspection Team consisting of officers of Drugs Control Administration, Andhra Pradesh, India for Export purpose.

This Certificate is valid for a period of Two years from the date of issue.

DIRECTORATE OF DRUGS CONTROL ADMINISTRATION GOVERNMENT OF ANDHRA PRADESH HYDERABAD

Yours faithfully,

21/9/12

JOINT DIRECTOR & LICENSING AUTHORITY
DRUGS CONTROL ADMINISTRATION

Copy to: The Deputy Director, Visakhapatnam District.

IPO MUMBAI 29-06-2015 16:03

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GOVERNMENT OF ANDHRA PRADESH
DRUGS CONTROL ADMINISTRATION

Office of the Director General,
Drugs and Copyrights,
Drugs Control Administration,
Vengalraonagar, Hyderabad – 038.

L.Dis.No.12836/M1A/Mfg/2012 Dated: 21 -09-2012

LIST OF PRODUCTS APPROVED UNDER WHO-GMP CERTIFICATION SCHEME FOR EXPORT PURPOSE

1.	OMEPRAZOLE PELLETS 8.5% W/W	USP/Ph.Eur
2.	LANSOPRAZOLE PELLETS 8.5% W/W	USP/BP
3.	ESOMEPRAZOLE MAGNESIUM TRIHYDRATE PELLETS 22.5% W/W	USP
4.	ITRACONAZOLE PELLETS 22% W/W	Ph.Eur
5.	FENOFIBRATE PELLETS 66% W/W	BP/USP

Manufacturer : M/s. Lee Pharma Limited,
Plot No.V, Phase-II, VSEZ,
Duvvada,
Sabbavaram (M)
Visakhapatnam District,
Andhra Pradesh, India.

When applicable : Placing the product on the market as detailed above

It is Certified that the above products have been authorized to be placed on the market for use in the Country.

Drug Licence No. : 33/VP/AP/2010/F/G dt: 15-07-2010,
In Form-25 valid upto 14-07-2015.

It is also Certified that (a) the manufacturing plant in which the products are produced is subject to inspection at suitable intervals.

The Unit M/s. Lee Pharma Limited, Plot No.V, Phase-II, VSEZ, Duvvada, Sabbavaram (M)Visakhapatnam District, Andhra Pradesh, India was inspected jointly by Sri.L.Pramod Reddy, Deputy Director, DCA, Visakhapatnam alongwith Sri.R.Chandra Shekhar, Assistant Director, Visakhapatnam and Smt.K.Rajitha, Drugs Inspector, DCA, Visakhapatnam of this Department on 06-07-2012.

The manufacturer conforms to requirement for Good Manufacturing Practices in the manufacture and quality control (As recommended by the World Health Organization) in respect of products mentioned above (Five numbers) for Export in the International market.

This Certificate is Valid for a period of Two years from the date of issue.

21/9/12

JOINT DIRECTOR & LICENSING AUTHORITY
DRUGS CONTROL ADMINISTRATION

DIRECTORATE OF DRUGS CONTROL ADMINISTRATION GOVERNMENT OF ANDHRA PRADESH HYDERABAD

IPO MUMBAI 29-06-2015 16:03

ANNEXURE-D

S. No.	Country	Application No.	Title	Status
01	India	2950/CHE/2007	A NOVEL PROCESS FOR THE PREPARATION OF CRYSTALLINE MAGNESIUM SALT OF (S)-OMEPRAZOLE DI HYDRATE	Pending
02	India	2382/CHE/2007	PROCESS FOR THE PREPARATION OF NOVEL SALT OF VORICONAZOLE OXALATE FORM C	Pending
03	India	2451/CHE/2010	NOVEL PROCESS FOR THE PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
04	PCT	PCT/IN2012/000121	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Published
05	U.S.A	13/820,568	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
06	Europe	12716665	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
07	China	2012/80009854.5	NOVEL PROCESS FOR PREPARATION OF LINEZOLID AND ITS NOVEL INTERMEDIATES	Pending
08	India	2450/CHE/2010	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
09	PCT	PCT/IN2012/000120	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Published
10	U.S.A	13/820,565	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
11	Europe	12716664.3	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
12	China	2012/80009872.3	ANHYDROUS LINEZOLID CRYSTALLINE FORM-II	Pending
13	India	1533/CHE/2009	IMPROVED PROCESS FOR THE PREPARATION OF OMEPRAZOLE FORM-A	Pending
14	India	1532/CHE/2009	AN IMPROVED PROCESS FOR PREPARATION OF CRYSTALLINE LANSOPRAZOLE	Pending
15	India	4256/CHE/2012	A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXYCARBONYL-3-HYDROXY]ADAMANTYLGLYCINE	Pending
16	PCT	PCT/IN2012/000865	A PROCESS FOR INDUSTRIAL PREPARATION OF [(S)-N-TERT BUTOXYCARBONYL-3-HYDROXY]ADAMANTYLGLYCINE	Published
17	India	5441/CHE/2012	A PROCESS FOR PREPARATION OF TRANS (1R,2R)-CYCLO HEXANE 1,2–DICARBOXYLIC ACID	Pending

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ANNEXURE-D

18	PCT	PCT/IN2013/000149	A PROCESS FOR PREPARATION OF TRANS (1R,2R)-CYCLO HEXANE 1,2–DICARBOXYLIC ACID	Published
19	India	5063/CHE/2013	NOVEL OXAZOLIDINONE COMPOUNDS	Pending
20	PCT	PCT/IN2014/000018	NOVEL OXAZOLIDINONE COMPOUNDS	Pending
21	India	2254/CHE/2014	NOVEL OXAZOLIDINONE ANTIBACTERIAL COMPOUND	Pending
22	PCT	PCT/IN2014/000497	NOVEL OXAZOLIDINONE ANTIBACTERIAL COMPOUND	Pending

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IPR, MUMBAI 29-06-2015 16:03

The Federation Of Andhra Pradesh Chambers Of Commerce & Industry

Estd. In 1917

(An ISO 9001:2000 Certified Organisation)

Award for 2005 - 2006

Excellence in Research and Development
(Small Scale Industry)
(Silver Rolling Trophy) - Instituted by Elico Ltd., Hyderabad

Presented to

Lee Pharma Ltd., Hyderabad

at the
89th ANNUAL AWARD FUNCTION
on 8th June, 2007

In recognition of their Research & Development in developing Innovative and cost effective simplified process for manufacture of Flumazenil, Anhydrous Olanzapine Form I and Clopidogrel Bisulfate Form I.

SUDHIR SANGHI
PRESIDENT

O.P. GOENKA
CHAIRMAN, AWARDS COMMITTEE

Annexure-E

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सत्यमेव जयते

TELEGRAM : SCINDRECH
दूरभाष/TEL : 26962819, 26567373
: 26565694, 26562133
: 26565687, 26562144
: 26562134, 26562122 (EPBAX)
फैक्स/FAX : 26960629, 26529745
Website : http:/www.dsir.gov.in

सूचना का अधिकार

भारत सरकार
विज्ञान और प्रौद्योगिकी मंत्रालय
वैज्ञानिक और औद्योगिक अनुसंधान विभाग
टेक्नोलॉजी भवन
नया महरौली मार्ग, नई दिल्ली – 110 016

GOVERNMENT OF INDIA
MINISTRY OF SCIENCE AND TECHNOLOGY
Department of Scientific and Industrial Research
Technology Bhavan
New Mehrauli Road, New Delhi - 110 016

BY SPEED POST

F.No.TU/IV-RD/2186/2012 **Dated: 16 November, 2012**

To,
M/s. Lee Pharma Ltd.
Sy. No.257 & 258/1, Door No.11-6/56
C-Block, Opp. IDPL Factory, Moosapet Vill.
Hyderabad - 500 037

Subject: **RENEWAL OF RECOGNITION OF IN-HOUSE R&D UNIT (S)**

Dear Sirs,

This has reference to your application for renewal of recognition of your In-House R&D unit(s) beyond **31-03-2012** by the Department of Scientific and Industrial Research.

2. This is to inform you that it has been decided to accord renewal of recognition to the In-House R&D unit of your firm at **Survey No.10/G-1, Gaddapotharam (Vill.), Jinnaram (Mandal), Medak (Dist.), A.P.** upto **31.03.2015.** Terms and conditions pertaining to this recognition are given overleaf.

3. Please acknowledge the receipt of this letter.

Yours faithfully,

(K.V.S.P. Rao)
Scientist – 'G'

IPO MUMBAI 29-06-2015 16:03

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TERMS & CONDITIONS OF REGISTRATION & RECOGNITION OF IN-HOUSE R&D U

01. On receipt of the recognition letter, the firm shall acknowledge by stating that they abide by the terms & conditions of the recognition.

02. In-house R&D units recognised by DSIR are also deemed to be registered. A separate certificate of registration** is issued along with the recognition letter. The recognition would be valid for the period specified in the recognition letter and application for renewal of recognition shall be submitted in the prescribed proforma at least 3 months before the expiry of the valid recognition. Failure to submit application in time may lead to automatic lapsing of the registration & recognition.
****However, the certificate of registration is not issued to R&D units of companies engaged in activities falling within the definition of 'hospital' as per notification No. 24/2007-Cus dt. 01.03.2007 and No. 16/2007-central excise dt. 01.03.2007 issued by Department of Revenue.***

03. The recognition given by DSIR, Ministry of Science & Technology is not transferable.
- In case there is a change in the location of R&D unit(s), the company should intimate DSIR forthwith returning the original documents along with a request to issue amended recognition letter and registration certificate, mentioning the new address.
- In case there is a change in the name of the company, it should intimate DSIR forthwith returning the original documents along with a request to issue amended recognition letter and registration certificate, mentioning the new name.

04. In case of merger/de-merger/amalgamations, the department should be intimated immediately. The company should also spell out/reiterate its policy towards R&D and submit an undertaking to continue the R&D activities, budgets, staffing, etc. along with necessary documents including legal documents such as court orders, ROC certificate/returns, if any, within one month failing which the company should apply for fresh recognition.

05. Separate accounts shall be maintained for each R&D unit and the consolidated expenditures shall be reflected in the audited statement of accounts in the Annual Report.

06. The company should submit a copy of its Annual Report within 15 days of its publication along with the annual return containing brief summary of achievements of the R&D unit(s), new products developed, processes developed/introduced, patents filed/granted, papers published, awards and prizes received and any other achievements to DSIR at the end of every year.

07. Commercial exploitation of the know-how/process developed by the in-house R&D unit(s) will be solely governed by the licensing policies of the Government, in operation from time to time and the decision of the licensing authorities.

08. The recognition by DSIR does not amount to approval under any section of Income Tax Act. Tax concessions, rebates, import concessions etc, if any, will be governed by the tax laws in operation from time to time. All such matters should be taken up by the company directly with the concerned authorities.

09. The registration will entitle the in-house R&D units to avail customs/excise duty exemption on purchase of equipment, instruments, spares thereof, consumables etc. used for research & development subject to relevant Government policies in force from time to time. Such exemptions will have to be separately applied for in the prescribed formats. The R&D units should also abide by the terms & conditions of the customs & central excise notifications issued/amended from time to time.

10. If special sale of equipment and products, prototypes, consumables, if any, accruing from the R&D activities should be intimated to DSIR immediately. The realisation, if any, from such sales/disposal/transfer of these items be shown in the R&D accounts of the firm as well as tax returns, as income of R&D unit. In case of special sale of R&D equipment, clearance from customs/excise authorities will also be required in view of the applicable notifications under which the equipment was imported/purchased in India.

11. Any violation of the terms & conditions mentioned above and/or provisions of taxation in force will make the firm liable to de-recognition.

12. The company will also conform to such other conditions for recognition contained in the Guidelines or as may be specifically prescribed in the recognition letter.

IPO MUMBAI 29-06-2015 16:03

Afzal Hasan

From: SecMD [secmd@leepharma.com]
Sent: 25, 04, 2015 11:09 AM
To: afzal@hasanandsingh.com
Cc: vatsala@hasanandsingh.com; avr@leepharma.com
Subject: Fw: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

From: SecMD
Sent: Saturday, January 17, 2015 10:36 AM
To: afzal@hasanandsingh.com
Subject: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Dear Sir,

FYKI.

Best Regards,
Mallika Balaji.

From: avr
Sent: Saturday, January 17, 2015 10:18 AM
To: Archana Shanker
Cc: 'Kramer, Sebastian' ; Archana Shanker ; Pravin Anand
Subject: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Dear Ms. Archana Shanker,

With reference to your below mail, we are awaiting further confirmation from your client.

Best regards,
Venkata Reddy Alla.

From: Archana Shanker
Sent: Friday, January 02, 2015 8:47 PM
To: avr

Cc: 'Kramer, Sebastian' ; Archana Shanker ; Pravin Anand
Subject: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Dear Sir/Ma'am,

On behalf of our client AstraZeneca AB, we acknowledge receipt of your letter dated 22nd November 2014 along with the complete annexures.

Our client is currently reviewing the same and will revert to you shortly.

Best regards,

Archana Shanker (Ms) | Anand And Anand
Sr. Partner & Head-Patents & Designs
Protection and Contentious (IPO & IPAB)

Enrolment No. : D-581/91
First Channel Building Plot No. 17 A Sector 16 A
Film City | Noida 201301 (UP) | India
Phone +91.120.4059300 | Fax +91.120.4243056 – 058
Archana@anandandanand.com | www.anandandanand.com

Registered Office:
B - 41, Nizamuddin East | New Delhi 110 013 | India

Asia IP Trademark Firm of the Year 2013, India
Chambers & Partners Band 1 firm in IP 2014, India
IAM 1000 Patent Gold ranked firm of the Year 2013, India
LEGAL500 First Tier firm Patent and Trademark practices, India 2014
Managing Intellectual Property- Tier 1 firm Trademark Prosecution; Trademark Contentious and Copyright, India 2013
Managing Intellectual Property- Tier 1 firm Patent Prosecution and Contentious 2014, India
WTR 1000 Gold ranked firm of the Year 2014, India

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All Anand and Anand e-mails & attachments are scanned for all known viruses at the time of transmission. Maximum attachment size permitted by our server is 10 MB.

From: avr [mailto:avr@leepharma.com]
Sent: 22 November 2014 12:03

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To: Kramer, Sebastian
Subject: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Covering letter

Dear Sir,

Please find the attached covering letter on the above subject.

Best regards,
Mallika Balaji.

Lee Pharma Ltd, Hyderabad, India

Lee Pharma Ltd, Hyderabad, India

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Afzal Hasan

From: Afzal Hasan [afzal@hasanandsingh.com]
Sent: 02, 03, 2015 5:09 PM
To: 'Archana@anandandanand.com'
Cc: 'Sebastian.Kramer@astrazeneca.com'; 'Pravin@anandandanand.com'; 'vatsala@hasanandsingh.com'
Subject: RE: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Importance: High

Dear Ms. Archana Shanker,

This refers to the License request by Lee Pharma Ltd. for manufacturing and selling Saxagliptin in India covered by Indian Patent No. 206543, as discussed in the trailing emails.

We hope that by this time your client, AstraZeneca AB must have completed reviewing the information and documents provided by Lee Pharma Ltd.

Now since two months have passed since your below email and about eight months have passed since Lee Pharma had sent its request for the license therefore, on behalf of our client Lee Pharma Ltd. we request you to take in on high priority and revert us with your client's views at the earliest, preferably before 7th of March 2015.

Thanks and Regards

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From: Archana Shanker
Sent: Friday, January 02, 2015 8:47 PM
To: avr
Cc: 'Kramer, Sebastian' ; Archana Shanker ; Pravin Anand
Subject: License request for manufacturing and selling Saxagliptin in India covered by Indian Patent no. 206543 - reg.

Dear Sir/Ma'am,

On behalf of our client AstraZeneca AB, we acknowledge receipt of your letter dated 22nd November 2014 along with the complete annexures.

Our client is currently reviewing the same and will revert to you shortly.

Best regards,

Archana Shanker (Ms) | Anand And Anand
Sr. Partner & Head-Patents & Designs
Protection and Contentious (IPO & IPAB)

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