**BEFORE THE CONTROLLER OF PATENTS**

**THE PATENTS ACT, 1970**

**SECTION 15**

In the matter of the Patents Act, 1970 (as amended)

& the Patents Rules, 2003 (as amended)

And

In the matter of Patent Application No 1220/MUMNP/2009 by

**JANSSEN PHARMACEUTICA N.V., Belgium**

And

In the matter representation by way of opposition

under Section 25 (1) of the Patents Act by

Network of Maharashtra people living with HIV, Laxmi Road, Pune-411002

And

Nandita Venkatesan and Phumeza Tisile, A-13, First Floor, Nizamuddin West, Delhi 110013

**D E C I S I O N**

1. On 29/06/2009, the Applicant filed a PCT National Phase application for a patent bearing number **1220/MUMNP/2009** in Patent Office, Mumbai entitled "FUMARATE SALT OF (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO)-ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL".
   A request for examination under section 11-B was filed on 23/04/2010, and was assigned a Request No. 1219/RQ-MUM/2010. As per the provision under Section 11-A of Patents Act, the said application was published on 14/08/2009.
   Accordingly, said application was examined under sections 12 and 13 of the Patents Act, 1970 (as amended) and the First Examination report (hereinafter referred to as FER) was issued on 12/03/2012. The applicant's agent filed the reply to the FER on 28/01/2013. After considering the reply in response to the FER, and the specification with amended claims 1-7 filed by the applicant's agent.
2. Meanwhile, two representations by way of opposition u/s 25 (1) of the Act (hereinafter referred to as the pre-grant opposition) were filed on 11/03/2013 and 07/02/2019 by Network of Maharashtra people living with HIV, Laxmi Road, Pune-411002 & Nandita Venkatesan and Phumeza Tisile, A-13, First Floor, Nizamuddin West, Delhi 110013

respectively, against the grant of patent to the invention in the subject application. Statement of grounds, prior art and comparison of patent application with prior art in the said pre-grant opposition are available in the e-dossier as document named "1220-MUMNP-2009-PRE-GRANT OPPOSITION(11-3-2013).pdf and 1220-MUMNP-2009-PRE GRANT OPPOSITION DOCUMENT [07-02-2019(online)].pdf

**3.** On 19-09-2013 "Network of Maharashtra people living with HIV" filed first pre-grant opposition and on 07-05-2022 "Nandita Venkatesan and Phumeza Tisile filed the 2nd Pre-grant opposition applicant's agent submitted reply Statements in support of the application under Rule 55(4) of the Patents Rules (as amended) to the representation by way of Oppositions by both of the Opponents , & the said documents available in the e-dossier as document named 1220-MUMNP-2009-PRE-GRANT OPPOSITION REPLY STATEMENT(19-9-2013).pdf, 1220-MUMNP-2009-Statement and Evidence [07-05-2022(online)].pdf & 1220-MUMNP-2009-Annexure [07-05-2022(online)].pdf.

4. After considering the reply filed in response to the first examination report by the applicant's agent and the report of the examiner on such reply, the cited documents along with the main grounds of the pre-grant oppositions, it was observed that the said patent application was not in order for grant. Keeping in view the provisions of the Patents Act, 1970 (as amended), a hearing notice under section 14 & 25(1) was issued to the applicant's agent as well as the opponent/opponent's agent vide email scheduled on 11/05/2022 through VC under rule 28(6) of the Patent Rules, 2003 (as amended) vide hearing notice dated 08/02/2022 which was adjourned to 15/06/2022 vide hearing notice dated 09/05/2022 as requested for adjournment of the scheduled hearing by filing a Request for Adjournment of Hearing under rule 129A of the Patents Rules, 2003 (as amended). Again, the scheduled hearing was adjourned as requested under rule 129A to 18/11/2022 vide hearing notice dated 24/08/2022. Further, adjournment requested on 09/11/2022 was not allowed. In respect of the said hearing notice dated 24/08/2022, a hearing was duly held on 18/11/2022 and attended by all the parties (Applicant's agent as well as opponent's agents), However hearing could not be concluded on the aforesaid date. In continuation of said hearing three subsequent hearings were held on 24/11/2022, 30/11/2022 & 17/01/2023(Which were requested by the way of representation by the agent of the opponent Nandita Venkatesan and Phumeza Tisile). Keeping in view the provisions of the Patents Act, 1970 (as amended) and with a view to provide natural justice to the applicant as well as to the both of the opponents sufficient opportunities were provided to hear all the arguments. Hearing Notice documents available in the e-dossier as document named 1220-MUMNP-2009-PreGrant-ExtendedHearingNotice-(HearingDate-18-11-2022).pdf and 1220-MUMNP-2009-PreGrant-ExtendedHearingNotice-(HearingDate-17-01-2023).pdf. Since all these documents are available in public domain, they are not reproduced here for the sake of brevity.

5. On the circumstances of the case, applicant's agent as well as opponent's agents appeared for hearing on the above scheduled date and all the objections (hearing notice u/ s 14) as well as grounds of opposition u/s 25(1) proceedings were discussed. the grounds on which opponent 1 (Network of Maharashtra people living with HIV) relied upon are considered carefully during the proceedings which are as below;

**PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS:-**

*Section 25 (1): Opposition to the patent where application has been published but not granted*: The following grounds and evidence set out the basis of the opposition to the application. It is submitted that the present application claiming invention is 'not an invention' within the meaning of Section 2(1)(j) of the Patents Act, and does not involve an inventive step as defined under section 2(1)(ja), as it is obvious to a person skilled in the art. It is further submitted that the present application is not a new invention as defined under section 2(1)(l) as it has been anticipated by publication before the date of filing of the patent application with complete specification and its priority date therein.

The Opponent has also opposed the Application for patent on the grounds laid under Sections 25(1)(b) as it has been prior claimed and published in the earlier application for which a patent has been granted, under Sections 25(1)(c) as the invention is prior claimed in India, under 25(1)(d) as the methods for making a derivative of quinoline in its salt form and the composition was known publicly, under 25(1)(e) as the invention claimed is obvious and clearly does not involve an inventive step, under Section 25(1)(f) as the claim made in the complete specification is not an invention within the meaning of the Patents Act and not patentable under section 3(d) the said Act and under Section 25(1)(h) read with section 8, as the applicant has failed to disclose information relating to foreign filing.

In any event, the Opponent is filing this pre-grant opposition on the grounds as stated under Section 25(1) of the Patent Act. The primary grounds of opposition are under Section 25(1)(b), (c), (e), (f) and (h) that

the invention so far claimed has been published before the priority date of the claim, in a specification filed in pursuance of an application for a patent or patent granted as stated in the following list of applications filed: Exhibit A {Patent No. 236811 granted on 23.11.2009 to the Applicant}, Exhibit B {*Preparation of Water-soluble compounds through salt formation*, known in the art}, Exhibit C and H {*Remington's Pharmaceutical Sciences* Chapters 89 and 90}; Exhibit D {EPO 575890 B1 the fumarate salt of a quinoline derivative}; Exhibit E {WO 92/10191 quinoline derivatives with pharmaceutical salts, esters, fumarate salts, etc.}, Exhibit F {*Optical Isomerism in Drugs* is known in the art}, Exhibit G and I {*The Theory and Practice of Industrial Pharmacy* Chapters 11 and 12} and *Exhibit J {US 5145684 Surface modified drug nanoparticles}* where the invention so claimed has been publicly known and claimed, and used prior to the priority date of the claims of the Applicant.

The Opponent states that none of the claims of the Applicant should be deemed accepted, unless the same are specifically admitted / accepted herein, and that the Opponent opposes all the claims of the Applicant as amended on 28.01.2013.

The grounds for opposition of claims 1 to 7 are primarily based on the provisions of section 25(1) of the Patents Act, as specified hereto.

(i) Claims 1 to 7 in the amended claims of the application for solid pharmaceutical composition comprising the fumarate salt of the compound TMC 207 and polyethylene glycol sorbitan fatty acid ester (Tween) as the wetting agent. At the outset it may be noted that the Applicant does not deserve a patent on the fumarate form of TMC 207, including the composition, as it has already been

claimed in an earlier application of the Applicant. The making of a fumarate salt of the compound including the solid pharmaceutical composition is obvious, known in the art and there is no novelty, invention or inventive step in making the same.

Claim 1 is for a solid pharmaceutical composition comprising of a pharmaceutically acceptable carrier and as an active ingredient the therapeutically effective amount of fumarate salt of TMC 207. However, the same has been claimed in the Patent application No. 220/DELNP/2005 for an application with title "a novel substituted quinoline compound" which was granted a patent being patent no. 236811 granted on 23.11.2009 [See internal pages 9 and 10 of Exhibit A] where acid additional salts and salt forms of TMC 207, including the fumaric acid has been claimed. Patent application No 220/DELNP/2005 also teaches pharmaceutical composition in tablets dosage form with glycols including process of making the pharmaceutical composition [See internal pages 13 and 14 of Exhibit A]. Therefore, this application 1220/MUMNP/2009 does not deserve a patent as it has already been claimed earlier and granted to the Applicant.

In any event, the salt form of a compound is not patentable in India. Section 3(d) of the Patents Act states that salt forms and derivatives of known substances are not patentable.

The art of preparation of water soluble compounds through salt formation is known and documented in the art. Numerous acids and bases are in use for providing the counter-ions to form salts. Salt formation usually improves the water solubility of acidic and

basic drugs because the salts of these drugs dissociate in water to produce hydrated ions. The degree of water solubility of salt depends on the structure of the acid or base used to form salt. All this is well documented in chemistry and known to a person skilled in the art.

The General Solubility Equation (GSE) has been developed and defined in the last two decades by Yalkowsky (since 1985) and his co-workers [See Yalkowsky, S.H. (1985) Solubility and solubilization of nonelectrolytes. In Yalkowsky, S.H. (ed.). *Techniques of Solubilization of Drugs.* Pp.1-14, Marcel Dekker, New York] using thermodynamically sound approach for establishing a semi-empirical correlation for the molar solubility of a solute, the octanol/ water partition coefficient from the structural formula and the melting point. Methods of ionization are known. Acqueous solubility is influenced and controlled by adjusting the pH of the solution via the equilibrium between the nonionized and isonized species, which has been explained in *"Preparation of Water-soluble compounds through salt formation"*, hereto annexed and marked as **"Exhibit B"**. The Applicant cannot claim a patent on these methods and compositions of salt forms that have been known in the scientific world for more than three decades.

The design of dosage forms lies in the field of the pharmaceutical technology but it also considered by the medicinal chemist while developing a drug from a lead compound. This is known and documented in pharmacology and medicinal chemistry. Drug substances are most frequently administered orally by means of

solid dosage forms such as tablets and capsules. The formation of solid forms has been known in the field of pharmacy and is well described in *Remington's Pharmaceutical Sciences,* the relevant portion of which is hereto annexed and marked as **"Exhibit C"**. [See Chapter 89 of *Remington's Pharmaceutical Sciences 1980,* page 1553 to 1584].

Drugs are usually administered topically or systemically. The routes have been classified in medicinal chemistry as being either parenteral or enteral. Parenteral routes are those which avoid the gastrointestinal tract (GI tract), the most usual method being intramuscular injection (IM). However, other parental routes are intravenous injection (IV), subcutaneous injection (SC) and transdermal delivery systems. Nasal sprays and inhalers are also parenteral routes. [See *textbook* of Thomas, G, Fundamentals of Medicinal Chemistry, Wiley Publications, 2003].

The enteral route is where drugs are absorbed from the alimentary canal (given orally, PO), rectal and sublingual routes. The route selected for the administration of a drug will depend on the chemical stability of the drug, both when it is across a membrane (absorption) and in transit to the site of action (distribution). Absorption is usually defined as the passage of the drug from its site of administration into the general circulatory system after enteral administration. The most common enteral route is by oral administration. Drugs administered in this way take about 24 hours to pass through the gastrointestinal tract (GI tract). Individual transit times for the stomach and small intestine

are about 20 minutes and 6 hours, respectively. Compounds may be absorbed throughout the length of the GI tract but some areas will suit a drug better than others. All this is well documented and known in medicinal chemistry and pharmacology [See *textbook* of Thomas, G, Fundamentals of Medicinal Chemistry, Wiley Publications, 2003]. All this is known, and the Applicant cannot claim a patent on these forms of administering drugs, as it obvious, anticipated and has been known in the art.

The degree of water solubility of a salt will depend on the structure of the acid or base used to form the salt. For example, acids and bases whose structures contain water solubilising groups will form salts with higher water solubility than compounds that do not contain these groups. For a chemist it is obvious if a drug is too water soluble it will not dissolve in lipids and so will not usually be readily transported through lipid membranes. This normally results in either its activity being reduced or the time for its onset of action being increased. It is known that the presence of a high concentration of chloride ions in the stomach will reduce the solubility of sparingly soluble chloride salts because of the common ion effect. This is known in the art, and methods of making salt forms of drugs are also known in the scientific field of pharmaceutical technology. [See *textbook* of Thomas, G, Fundamentals of Medicinal Chemistry, Wiley Publications, 2003]

Numerous acids and bases are in use for providing the counterions to form salts. Some acids and bases like hydrochloride mineral

acid is used more frequently than others like fumarate organic acids for use in drug salts of prescription products. The number of organic bases usable as salt formers is much smaller, because generally, amines and other nitrogen bases have their own pharmacodynamic activity, unless they are very rapidly metabolized. Exceptions are the essential basic amino acids, eg. Arginine and lysine. Even though fumarate acid is not used as often as hydrochloride acid in making salt forms of pharmaceutical drugs, it, including solid pharmaceutical compositions, has been used and has been known in the art much prior to the Applicant's priority date. [See Chapter 35, Stahl P. Heinrich, *"Preparation of Water-soluble compounds through salt formation"* internal pages 606 to 608, 610 "The Practice of Medicinal Chemistry" edited by Camille Georges Wermuth, second edition 2003, at Exhibit B].

Further, Fumaric acid forms of quinoline derivatives have been known for many years. Fumaric acid has been used for a quinoline derivative drug used for MDR cancer in 1993, hereto annexed and marked as **"Exhibit D"**, is a copy of European Patent No. EP0575890 (B1) that relates to quinoline derivatives of fumarates having a stimulating activity on the carcinostatic effect. The said EP patent at Exhibit D shows that fumarate salts of quinoline derivatives can be made and have been known much prior to the priority date of the Applicant herein. The EP patent also displays that quinoline derivatives are known to have properties useful for treating multi-drug resistant ailments. Therefore, the Applicant

does not deserve a patent, and the application should be dismissed. [See Pages 2, 3 of Exhibit D].

In another PCT Application being WO92/10191, the relevant portion of which is hereto annexed and marked as **"Exhibit E"**, quinoline derivatives have been claimed, along with their pharmaceutically accepted salts and esters, including the fumarate salt, and the use of wetting agents is used, and solid and other forms of the drugs are made. Therefore, the making of fumarate salt form of a quinoline derivative, the use of wetting agents and making solid forms of the drug for oral administration is known in the art, much before the priority date of the Applicant, and the Applicant does not deserve a patent. [See WO 92/10191, "Quinoline, napthyridine and pyridobenzoxazine derivatives," internal pages 2, 13 to 19 of Exhibit E].

The Applicant has also made claims for a patent on isomers (alpha S and beta R) of TMC 207. It needs to be noted once again, that the alpha and beta forms of TMC 207 have already been claimed in the earlier application of the Applicant, for which the patent has been granted, being Patent No. 236811. [See internal pages 10-11 of Exhibit A].

Further, optical isomerism in drugs has been known in the art, is obvious and well documented prior to the priority date of the Applicant. Hereto annexed and marked as **"Exhibit F"** is a copy of an article written by Camille G. Wermuth on *Optical Isomerism in Drugs*. The article reveals that racemates and/or enantiomers have been known to a person skilled in the art their

pharmacological activity, activity ratio is known and documented. The isomeric activity ratio of a highly active couple of isomers is superior to that of a less active couple is known and documented since 1956. There is no invention, inventive step in the use of chiral centres, isomer, enantiomers and racemates as claimed by the Applicant herein. [See Camille G. Wermuth, Chapter 17, "*Optical Isomerism in Drugs,*" from "The Practice of Medicinal Chemistry" edited by Camille Georges Wermuth, second edition 2003, pages 275, 278, 282 and 284-285 at Exhibit F].

Claims 2 to7 relate to oral administration of the solid pharmaceutical composition, the weight based composition based on the active ingredient, wetting agent, diluents, glidant. The claims are also for the pharmaceutical composition being in the tablet form weight based of the tablet core with polymer, disintegrant, lubricant, etc. The Applicant is claiming a patent on the pharmaceutical composition having the active ingredient along with diluents such as lactose, maize starch; binder coating such as hypromellose; wetting agent such as polysorbate; disintegrant such as croscarmellose sodium; glidant such as colloidal silicon dioxide and lubricant such as magnesium stearate. The Applicant is also claiming a patent on film – coated forms of the pharmaceutical composition in tablet and other forms.

The Opponent humbly states that making solid forms, tablets, powders, film coating is obvious, anticipated and known to a person skilled in the art ever since pharmaceutical drugs have been made suitable for oral administration. There is no inventive

step, invention or novelty in the same. In any event, the Applicant appears to be claiming a patent for the percentage of the ingredients, wetting agent, etc. in the tablet, solid and other forms of the pharmaceutical composition. However, such permutations and combinations are also known, anticipated and obvious to a person skilled in the art, and there is no inventive step or novelty in the same. It is submitted that the selection of particular range of ingredients from the ranges already known in the prior art in this case cannot amount to establish the inventive step and variations in the amounts of the known ingredients appear merely workshop improvements achieved by a person skilled in the art without performing any substantial experiments and cannot be said a technical advancement of an existing knowledge which is required by the definition of the "inventive step" as mentioned in section 2(1)(ja) of the Patents Act, 2005.

) Making of solid forms, tablets, etc. and use of ingredients as stated in the Application have been used and known to a person skilled in the art, and therefore no patent can be granted to the Applicant. [See *Remington's Pharmaceutical Sciences 1980*, Chapter 89, page 1553 – tablet, capsules and pills at Exhibit C.]

i) Further, the formula/ composition of the tablet, the various ingredients as claimed in claims 2-7 are known in the art and are commonly used excipients for tablet manufacturing. Hereto annexed and marked as **"Exhibit G"** is a copy of the relevant pages of the book *"The Theory and Practice of Industrial Pharmacy"* by Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig [See

Chapter 11, page 321 of Exhibit G, 3rd Edition, 4th Indian Reprint-**1991**] that describes the commonly used excipients wherein *lactose, starch and microcrystalline cellulose* as diluents; *Magnesium stearate* (written as stearic acid derivative in this book) is mentioned as lubricants; *Colloidal Silicon dioxide* (written as "silica derivative in this book) is mentioned as glidants and flow promoters. *Croscarmellose sodium* (written as Ac-Di-Sol in this book) is mentioned as a tablet disintegrant. [See Chapter 11 on page 328 of Exhibit G].

Film coating of tablets and drugs have been known and obvious in the field of pharmacy for centuries. Hereto annexed and marked as **"Exhibit H"** is a copy of the relevant portions of *Remington's Pharmaceutical Sciences* [See Chapter 90, pages 1585-1593, at page 1589 of Exhibit H] that describes the coating of pharmaceutical dosage forms and the use of polymer-coated tablets.

Also, hereto annexed and marked as **"Exhibit I"** is the relevant portions of *The Theory and Practice of Industrial Pharmacy* [See Chapter-12, pages 346-373, at page 359, 362 and 365 of Exhibit I], describes tablet coating technology, wherein the tablet coating principles, the coating processes, equipments, etc. have been described in details. Film coating and use of *Hypromellose* (written as hydroxypropyl methyl cellulose in this book) is listed in the examples showing the cellulose aqueous formula, hydroxypropyl methyl cellulose is also described as a film former.

In any event, the US Patent No. 5145684 granted on 8.9.1992, which is hereto annexed and marked as **"Exhibit J"**, discloses the use of wetting agents (also called surface modifiers) such as polyoxyethylene sorbitan fatty acid esters (commercially available a Tween) together with the poorly soluble active agents and excipients. The object of the invention in US 5,145,684 is to provide pharmaceutical compositions having enhanced bioavailability. The bioavailability of poorly soluble active agent such as anti-mycobacterial agents are increased by decreasing particle size and using wetting agents. As such, the present application deserves to be rejected under Sec. 25(1)(e) read with Sec. 2(1)(ja) for being obvious and lacking in inventive step.

As stated above, there is no inventive step, invention, novelty in making a salt form of a compound, and in making it in solid forms or tablet form and coating it with a film for oral absorption. The procedure for making salt forms, making solid forms, making tablets, and film coated pharmaceutical compositions have been known in the art for decades, and is obvious to a person skilled in the art and the Applicant's patent application should be dismissed *in limine.*

Thus, for all the above stated reasons the Patent Application 1220/MUMNP/2009 ought to be rejected in its entirety. As permitted under Section 25(1) of the Patents Act read with Rule 55(1) of the Rules, the Opponent requests that the Patent Office informs the Opponent immediately of any response filed by the Applicant to this Opposition and

also grant the Opponents a hearing in the present matter. The Opponents also request the right to be able to submit further documents, evidence, as and when necessary, in order to further substantiate the grounds of opposition herein and to oppose any amendments or changes that the Applicant may make to the Complete Specifications or claims.

. The Opponent reiterates the Right to Health as paramount importance, and states that such applications for patents that are not novel, known to a person skilled in the art and non-inventive ought to be rejected.

. The Opponent submits that the derivative of quinoline, called TMC 207 also known as Bedaquiline, which is the compound under consideration in the present application, has unfortunately received a patent in India. Though there is no inventive step, invention or novelty in the making of TMC 207, as the properties of quinoline derivatives have been known for years, including the bromination of quinoline, and the use of quinoline as anti-tuberculosis has also been known. Quinoline derivatives have also been used in multidrug resistant cases for cancer and antibiotic resistant infections caused by bacteria, fungi, mycobacteria. Therefore, the use of quinoline derivative in MDR tuberculosis is not an unknown property of quinoline or its derivatives. Nevertheless, it recently got approval from the USA FDA to be used for MDR Tuberculosis. Making the pharmaceutical compound into a suitable salt form and in a suitable form for oral absorption or administration through oral or other routes is known in the art and obvious. There is no invention, inventive step or novelty in the present patent application.

.. The Opponent states that the Patent application ought to be rejected as there are various claims and publications, as stated above, before the

**priority** date of the Applicant herein. In any event, the Opponent states that the subject matter of the application is **anticipated** by the earlier patents granted and earlier publications, and the known art of making a salt form of a pharmaceutical compound.

. Further, the invention so far claimed **does not involve an inventive step and is obvious** to a person skilled in the art. Therefore, provisions of sections 2(1)(j), (ja) and (l) are attracted read with section 25(1)(e) and (f). The Opponent states that making a salt form of a pharmaceutical compound, including making it in a form for oral consumption along with wetting agent in tablet, film coated form are **not an invention** and do not require an inventive step, as it is known and used commonly and obvious to a person skilled in the art. There is a **lack of novelty**. The claims of the applicant for patenting a pharmaceutically acceptable salt, diluents, carrier or excipient of the composition is **not patentable** in India under **section 3(d)**. There is no synergism, and the compound so claimed is a mere ad-mixture and not patentable under **section 3(e)** of the Patents Act.

. Thus the patent application ought to be rejected under section 25(1) read with section 3 of the Patents Act.

. Furthermore, it is submitted that as per Section 8, the Applicant prosecuting an application for a patent in any country outside India in respect of the same or substantially the same invention ought to disclose the same to the Controller and give an undertaking to keep him informed about subsequent filing and prosecution of such application up to the grant of the Patent. It is submitted that the Patent Applicant has failed to inform of the status of the application being prosecuted in foreign

countries. It is submitted that while corresponding Final Rejection has been issued against US Patent Application published as US2010028428 on 25.07.2012, a post-grant opposition has been filed against EP2086940. The Ld. Examiner / Controller are requested to please take note of the same. It is submitted that the present patent application ought to be rejected on the ground of 25(1)(h) alone.

The Opponent therefore prays:-

(a) That the patent application 1220/MUMNP/2009 claiming a patent on "Fumarate Salt of (Alpha and Beta R)- 6- Bromo -Alpha (2- Dimethylamino) – ethyl – 2- methoxy- alpha- 1- Naphthalenyl- Beta- Phenyl 3- Quinolineethanol" ought to be rejected *in toto*;

(b) That the Opponent be granted a hearing under section 25(1) read with Rule 55(1) and the Opponent be informed immediately of any response filed by the Applicant to this Opposition;

(c) That the Opponents be allowed to submit further documents, evidence, as and when necessary;

(d) That the Opponent be allowed to oppose with documents and further evidence any amendments or changes that the Applicant may make to the Complete Specifications or claims;

(e) For costs;

(f) For such other and further orders that may deem necessary in the circumstances.

6. **Further** opponent 2, Nandita Venkatesan and Phumeza Tisile relied upon are considered carefully during the proceedings which are as below;

1. That the invention claimed in any and all claims of the complete specification was published before the priority date of the claim in India or elsewhere in any other document – Section 25(1)(b);

2. That the invention claimed in any and all claims of the complete specification is obvious and clearly does not involve any inventive step – Section 25(1)(e);

3. That the subject of any and all claims of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act – Section 25(1)(f);

4. That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed- Section 25(1)(g);

5. That the Applicant did not disclose information required by Section 8– Section 25(1)(h).

**Detailed Grounds**

**CLAIMS 1 TO 7 ARE NOT NOVEL, AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(1)(e) OF THE PATENTS ACT**

Section 2(1) (j) of the Patents Act defines an "invention" as "a new product or process involving an inventive step and capable of industrial application". Section 25 (1)(b)(ii) of the Patents Act allows opposition of a patent if the alleged invention, as claimed in any claim of the complete specification has been published before the priority date of the claim in India or elsewhere, in any other document.

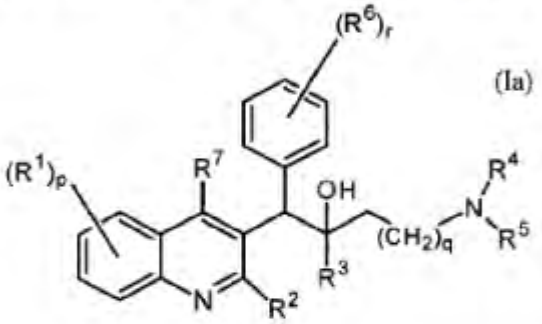
Therefore, claims of a patent application are to be rejected if a publication dated before the priority date of the application in question discloses the alleged invention. Disclosure of alleged invention by such a document may be determined by comparing the claims of the patent application in question to the disclosures in the prior art, read in light of the general knowledge available to a person skilled in the art.

It is the Opponent's claim that document published before the date of priority of the Present Application discloses the compounds of claims 1-7. Therefore, claims 1-7 should be rejected for lack of novelty.

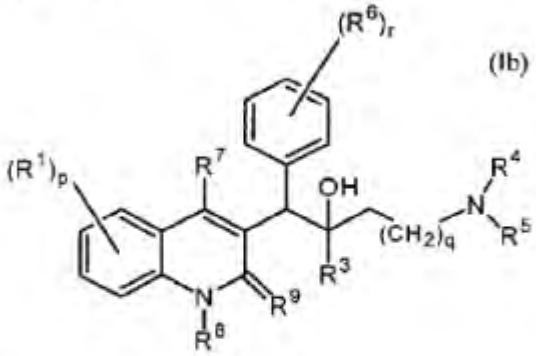
The Opponent relies on PCT publication no. WO 2004/011436 (hereinafter "WO '436"), published on February 5, 2004 viz. much before the priority date of the Present Application viz. 05.12.2006. WO '436 may be relied on as a prior art document. WO '436 is annexed herein as **Exhibit-A.**

WO '436 is a patent publication titled "*Quinoline derivatives and their use as mycobacterial inhibitors*" and was filed on 18.07.2003 by the Applicant of the Present Application, viz. Janssen Pharmaceutica N.V.

WO '436 states that it discloses an invention related to novel substituted quinoline derivatives according to formulae Ia and Ib (reproduced below) (see abstract of WO '436 and internal page 3 of WO '436)



(Ia)



(Ib)

In fact, the Applicant itself has admitted that Enantiomer (alpha S, beta R)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol corresponds to compound 12 (A1 enantiomer) in WO2004/011436 and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis (see internal page 2 of the complete specification of present application, lines 21-24);

Further, WO '436 states that the invention includes "*pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof*" of the above disclosed compounds. (See WO'436 at abstract at lines 1-3, and claim 1 at internal page 52)

WO'436 is stated to claim compounds that is particularly useful in the treatment of *Mycobacterium tuberculosis* (See WO'436 abstract at lines 3-4 and internal page 1 at lines 5-8)

WO'436 indicates that pharmaceutically acceptable salts could be obtained by treating the base form of the compounds (Ia or Ib) with appropriate inorganic acids or organic acids such as fumarate acid (see internal page 8, lines 30-38, and internal page 9 at lines 1-4).

WO'436 particularly discloses that the invention therein relates to a composition. It states, "*The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral*

*compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included... Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition. The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.*" (emphasis supplied) (see internal page 12, lines 3-36, internal page 13, lines 1-4).

Therefore, as seen above, WO'436 discloses:

- pharmaceutical composition comprising compound Ia or Ia, including compound 12, viz. (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol;
- Such composition could include additional salt form of compound 12, including a fumarate salt form;
- Such composition includes the active ingredient (such as compound 12) combined with a pharmaceutically acceptable carrier;
- Such composition may include additional ingredients including a surfactant, often used as a wetting agent;
- The composition will preferably contain 0.1 to 70 % by weight of the active ingredient;
- The composition will preferably contain 30 to 99.9 weight % of a pharmaceutically acceptable carrier.

WO'436 also teaches process for separating the racemic mixtures of enantiomers produced using the process described therein. It notes that, "*The racemic compounds of either Formula (Ia) and (Ib) may be converted*

*into the corresponding diastereomeric salts forms by reaction with a suitable chiral acid.*" (See WO'436, internal page 10, lines 23-28).

A tabular form of comparison between the disclosure in WO '436 and the claims of the present application is indicated below:

| **Claims of the Present Application** | **Disclosure in WO '436** |
|---|---|
| Claim 1<br>A solid pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol and further comprising a wetting agent, said wetting agent being a polyethylene glycol sorbitan fatty acid ester. | A composition comprising fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol (also known as 1 -(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen- 1 -yl- 1 - phenyl-butan-2-ol) and wetting agent is disclosed, as can be seen from the relevant portions of WO'436 disclosed below:<br><br>Claim 6: "*A compound according to claim 1, characterized in that the compound is :… 1 -(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen- 1 -yl- 1 - phenyl-butan-2-ol...*" (See WO '436, internal page 55)<br><br>Claim 8: "*A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically* |

| | |
|---|---|
| | *effective amount of a compound as defined in any one of claims 1 to 7.*" (WO '436, internal page 56)<br><br>"*Most preferable, the compound is :...*<br>*o 1 -(6-bromo-2-methoxy-quinolin-3 -yl)-4-dimethy lamino-2-naphthalen- 1 -y 1- 1 - phenyl-butan-2-ol ;... the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof.*" (See WO '436, internal page 8, lines 13-14, 27-29)<br><br>"*Some acid addition salts can be obtained by treating the base form of the compounds with...fumaric acid*" (See WO '436, internal page 8, lines33-34, internal page 9, line 1)<br><br>*"The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the* |

| | |
|---|---|
| | *invention... For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycol...*" (See WO '436, see internal page 12, lines 3-23)<br><br>"*The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.*" (internal page 13, lines 1-4) |
| Claim 2<br>A pharmaceutical composition according to claim 1 wherein the composition is suitable for oral admission. | WO'436 also discloses that the composition may also be used for oral admission as seen below.<br>"*These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection.*" (See WO '436, internal page 12, lines 13-15) |
| Claim 3<br>A pharmaceutical composition | WO'436 also discloses the range of the constituent ingredients by |

| | |
|---|---|
| according to claim 1 or claim 2 comprising by weight based on the total weight of the composition:<br>(a) From 5 to 50% of active ingredient;<br>(b) From 0.01 to 5% of a wetting agent;<br>(c) From 40 to 92% of a diluent;<br>(d) From 0.1 to 5% of a glidant. | weight in the composition as disclosed below:<br>"*Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight of the active ingredient, and, from 1 to 99.95% by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.*" (See WO '436, internal page 12, lines 31-36)<br><br>"*The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.*" (See WO'436, internal page 13, lines 1-4) |
| Claim 4<br>A pharmaceutical composition according to any one of claims 1 to 3 wherein the composition is in the | WO'436 also discloses that the composition may be in the form of a tablet, as has been shown below.<br>"*Examples of such unit dosage* |

| | |
|---|---|
| form of a tablet. | *forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.*" (See WO '436 at internal page 13, lines 11-13) |
| Claim 5<br>A pharmaceutical composition according to claim 4 comprising by weight based on the total weight of the tablet core<br>a) from 5 to 50% of active ingredient;<br>b) from 0.01% to 5% of a wetting agent;<br>c) from 40 to 92% of a diluent;<br>d) from 0 to 10% of a polymer;<br>e) from 2 to 10% of a disintegrant;<br>f) from 0.1 to 5% of a glidant;<br>g) from 0.1 to 1.5% of a lubricant. | WO'436 discloses the weight by percentage of the constituents of the composition, as disclosed below:<br>"*Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight of the active ingredient, and, from 1 to 99.95% by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.*" (See WO '436, internal page 12, lines 31-36)<br><br>"*The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant,* |

| | |
|---|---|
| | *stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.*" (See WO'436, internal page 13, lines 1-4) |
| Claim 7<br>A pharmaceutical composition according to any one of claims 4-6 which is film-coated. | WO'436 not only discloses that the composition could be in tablet form bit also discloses that such a tablet could be also coated. This can be seen in the portion reproduced below.<br>*"Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.*" (See WO'436, internal page 13, lines 11-13) |

Hence, WO'436 discloses-

- the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol;
- a composition comprising the fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol and a pharmaceutical carrier;

- a composition of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol and the pharmaceutical carrier by weight in tablet form;
- Composition as above mentioned with a wetting agent;
- Composition as above mentioned in a coated tablet form;
- Suitability of such composition for oral administration.

Therefore, it is submitted that WO'436 discloses all the elements of the claims 1-7 of the Present Application. Hence, Claims 1 to 7 of the Present Application should be rejected under Section 25(1) (b) (ii) of the Patents Act on grounds of anticipation by prior publication.

**CLAIMS 1-7 OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(e) OF THE PATENTS ACT, ON GROUND OF LACKING INVENTIVE STEP AS DEFINED UNDER SECTIONS 2(1)(ja) OF THE PATENTS ACT**

It is submitted that Section 2(1) (j), Patents Act defines an "invention" as "*a new product or process involving an inventive step and capable of industrial application*" (emphasis supplied). For an alleged invention to qualify for a patent, it must involve an inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as "*a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art*".

Section 25(1)(e) of the Patents Act provides that an application may be opposed if the alleged invention is obvious and does not involve an inventive step having regard to matter published in India or elsewhere in any document before the priority date of the alleged invention. Without prejudice to other grounds raised herein, the Opponent submits that claims 1-7 of the Present Application lack an inventive step and therefore should be rejected.

It is submitted that at the priority date of the Present Application, as will be explained below, the following were well known to persons skilled in the art:

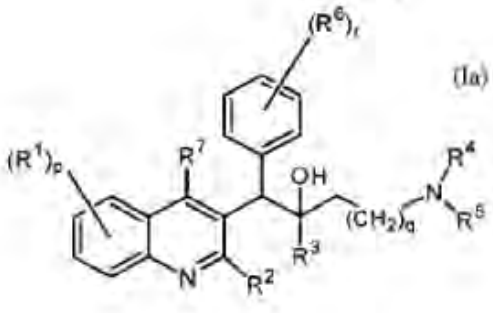
fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol;

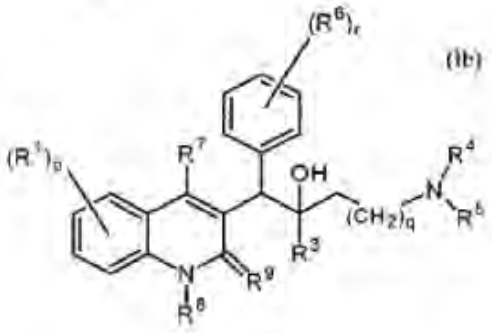
a composition of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol and the pharmaceutical carrier in tablet form;

Composition of fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol with constituents including lactose monohydrate, hypromellose, polysorbate 20, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

**Composition comprising Fumarate salt of (alpha S, beta R)- 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-napthalenyl-β-phenyl-3-quinolineethanol was known**

The Opponent relies on WO'436 (Exhibit-A) again. It is submitted that WO'436 discloses the use of Formulae Ia and Ib as antimycobacterial agents and the method of using the same for treatment of mycobacterial infection, particularly, M. tuberculosis (See WO'436 at page 2, lines 20-24). The structures of Ia and Ib are reproduced below for easy reference:



Further, it is submitted that WO'456 discloses a composition comprising as an active ingredient, a therapeutically effective amount of a compound, which includes compounds of formula 1(a) or 1(b) and a pharmaceutical carrier. (See WO'436, internal page 12, lines 4-13).

It is submitted that WO '436 also discloses pharmaceutically acceptable acid or base addition salts of formulae Ia and Ib. (See WO'436 at abstract and claim 1 of WO'436 at internal page 52). Such acid salts include those obtained by treating compounds (Ia or Ib) with appropriate inorganic acids or organic acids such as fumaric acid (see internal page 8, lines 30-38, and internal page 9 at lines 1-4). In fact claim 6 of WO'436 claims, "*a compound according to claim 1, characterized in that the compound is…1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol…the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof.*" The stereoisomeric form of *1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol* would include (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol, the active ingredient claimed the composition claimed in the Present Application.

Therefore, on the date of priority of the Present Application, fumarate salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol was known.

It is submitted that the Applicant of the Present Application has admitted that enantiomer (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol corresponds to compound 12 (A1 enantiomer) in WO'436.

WO'436 also discloses a composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of compounds Ia or Ib. WO'436 indicates that the composition in unitary dosage form can be administered orally or by parenteral injection. WO'436 also indicates that

pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols could be used in preparation of oral liquid preparations, and that solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents can be used for powders, pills, capsules and tablets (see WO'436, internal page 12, lines 3-30).

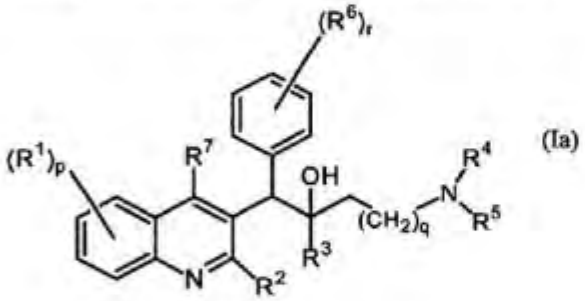
WO'436 also discloses the amount by weight of the components of the composition where it provides, *"Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition. The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant."* (See WO'439 internal page 12, at lines 31-36 and page 13, lines 1-4). Further, this document also teaches a film coated tablet of the composition (See WO'436, internal page 13, lines 11-13).

Thus a person skilled in the art (POSITA) on reading WO'436 would be taught a composition comprising *inter alia* fumarate salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol along with pharmaceutical media. The POSITA will also be taught the composition by weight of the pharmaceutically active ingredient and the pharmaceutically acceptable carrier. The POSITA would also be taught that other ingredients including a surfactant (wetting agent) could be used in such a composition.

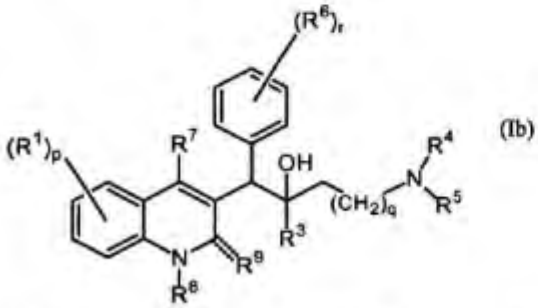
The Opponent relies on the publication WO/2005/117875 (hereinafter "WO '875" and annexed herewith as **Exhibit-B**) titled "*Use of substituted quinoline derivatives for the treatment of drug resistant mycobacterial*

*diseases*", filed in the name of the Applicant of the Present Application. WO'875 was published on 15.12.2005 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO '875 may be relied on as a prior art document.

WO'875 relates to the use of a substituted quinoline derivative for preparing medicament for treating a drug resistant Mycobacterium strain. This is done so using a substituted quinoline derivative according to Formula (Ia) or Formula (Ib) the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof. WO'875 also discloses a composition comprising a pharmaceutically acceptable carrier, therapeutically effective amount of compounds (Ia) or (Ib) and one or more other antimycobacterial agents. (See WO'875 at abstract and internal page 3 at lines 15-20). The structures of compounds (Ia) and (Ib) are reproduced below for reference:




(Ia)

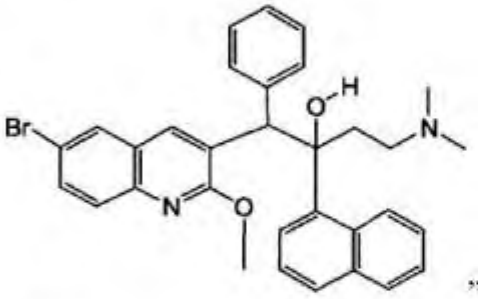



(Ib)

WO'875 discloses that, "*An interesting group of compounds are the compounds according to Formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically 1-(6-bromo-2-methoxy-quinolyn-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol corresponding to 6-bromo-α-[2-(dimethylamino)ethyl]-2-*

*methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol; a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a N-oxide form thereof.*" (See WO'875, internal page 13, line 36-37 and internal page 14, lines 1-5)

WO'875 further discloses that, "*An alternative chemical name for l-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-l-yl-l-phenyl-butan-2-ol is 6-bromo-α-[2-(dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol. Said compound can also be represented as follows :*




" (See WO'875, internal page 14, lines 6-14)

Further, it notes that most preferably the compound is, "*...(αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt thereof...*" (See WO'875 at internal page 14, lines 14, 24-26). (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol has also been identified as the most preferable compound (See WO'875, internal page 15, lines 1-5). It also discloses that this compound is useful for the treatment of drug-resistant mycobacterium strain (See WO'875, internal page 18, lines 14-34, internal page 19, lines 1-2).

WO'875 also discloses that pharmaceutically acceptable acid addition salts of compounds (Ia) or (Ib) can be formed by treating their base forms with

appropriate acids, including fumaric acid. (See WO'875, internal page 15, lines 8-16).

WO'875 also teaches that the compounds of formula (la) and (lb) may be synthesized in the form of racemic mixtures of enantiomers. It indicates that these mixtures can be separated based on known resolution procedures. Further, it indicates that, "*The racemic compounds of either Formula (la) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either Formula (la) and (lb) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation.*" (See WO'875 at internal page 17, lines 9-21)

In fact, use of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, i.e. compound 12, or a pharmaceutically acceptable acid addition salt in a composition with other antimycobacterial agents has been suggested (See WO'875, internal page 19, lines 19-35)

WO'875 also discloses that, "*These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the*

*case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms in which case solid pharmaceutical carriers are obviously employed.*" (See WO'875, internal page 21, lines 28-37). Further, such composition may also contain a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant (WO'875, internal page 22, lines 35-36 and internal page 23, lines 1-2).

That is, on reading WO'875, a POSITA would be taught about a composition comprising (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, a pharmaceutically acceptable carrier in a tablet form.

WO'875 also discloses identification of the stereoisomer and states, "*Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.*" (See WO'875, internal page 23, lines 21-31).

Further, it discloses the boiling point of stereoisomer A1, (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol viz. compound 12 (see internal page 25, entry 13).

WO'875 also discloses the minimum inhibitory concentration (MICs) of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol against different clinical isolates

of resistant Mycobacterium strains, as reproduced below (see internal pages 35-36):

Table 7 :

| Strains | Rifampin | Compound 12 | Compound 109 | Compound 2 |
|---|---|---|---|---|
| *M.tuberculosis* isoniazid-resistant low level | 0.5 | 0.06 | 0.12 | 0.25 |
| *M.tuberculosis* isoniazid-resistant high level | 0.5 | ≤ 0.01 | 0.03 | ≤ 0.01 |
| *M.tuberculosis* rifampin-resistant | >256 | 0.06 | 0.12 | 0.06 |

Table 8:

| Strains | Rifampin | Compound 12 |
|---|---|---|
| *M.tuberculosis* isoniazid-resistant High Level | 0.25 | 0.01 |
| *M.tuberculosis* isoniazid-resistant high level | 0.5 | 0.06 |
| *M.tuberculosis* isoniazid-resistant high level | 0.12 | 0.03 |
| *M.tuberculosis* isoniazid-resistant high level | ≤ 0.06 | 0.01 |
| *M.tuberculosis isoniazid*-Resistant high level and streptomycin-resistant | 0.25 | 0.01 |
| *M. tuberculosis* rifampin-resistant | 256 | 0.03 |
| *M.tuberculosis* rifampin-resistant | 16 | 0.03 |
| *M.tuberculosis* rifampin-resistant | 256 | 0.01 |
| *M.tuberculosis* streptomycin-resistant | 0.5 | 0.01 |
| *M.tuberculosis* ethambutol-resistant | 0.25 | 0.01 |
| *M.tuberculosis* pyrazinamide-resistant | 0.5 | 0.03 |

Further, WO'875 discloses the minimum inhibitory concentration (MICs) of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol against different clinical isolates of Mycobacterium strains resistant to fluoroquinolones as indicated below (see internal page 37)

Table 9 :

| Strains | Rifampin | Compound 12 | Ofloxacin |
|---|---|---|---|
| *M.tuberculosis* | 1 | 0.06 | 8 (Ala83Val Ser84Pro)* |
| *M.tuberculosis* | 2 | 0.12 | 32 (Asp87Gly)* |
| *M.avium* | 16 | 0.007 | 128 (Ala83Val)* |

* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance

Table 10 :

| *Strains* | *Rifampin* | *Compound 12* | *Ofloxacin* |
|---|---|---|---|
| *M.smegmatis* | 64 | 0.01 | 8 (Asp87Gly)* |
| *M.smegmatis* | 64 | 0.01 | 32 (Ala 83 Val and Asp87Gly)* |
| *M.smegmatis* | 64 | 0.01 | 32 (Ala83Val and Asp87Gly)* |
| *M.smegmatis* | 128 | 0.007 | 2 (Ala83Val)* |
| *M.smegmatis* | ND | 0.003 | 32 (Asp87Gly)* |
| *M.fortuitum* | 128 | 0.01 | 1 |
| *M.fortuitum* | 128 | 0.007 | 1 (Ser84Pro)* |
| *M.fortuitum* | >64 | 0.01 | 1.5 (Asp87Gly)* |

* The indications between parentheses indicate the mutations in the protein responsible for ofloxacin resistance.

Claim 13 of WO'875 claims, "*Use according to claim 1, characterized in that that compound is selected from the group consisting of:..1-(6-bromo-2-*

*methoxy-quinolin-3-yl)-4-dimethylamino-2-napthalen-1-yl-1-phenyl-butan-2-ol…a pharmaceutical acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, a tautomeric form thereof or a N-oxide form thereof.*" (See WO'875 at internal page 47)

Further, claim 16 also claims, "*Use according to claim 15 wherein the compound is 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, or a pharmaceutically acceptable acid addition salt thereof.*"(See WO'875 at internal page 48).

In particular claim 19 claims,"*(αS,βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol, or pharmaceutically acceptable acid additional salt thereof.*" (See WO'875 at internal page 48)

Claim 25 therein also claims, "*A pharmaceutical composition comprising pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of (a) a compound of formula (Ia) or (Ib) as defined in any one of claims 1 to 20 and (b) one or more other antimycobacterial agents.*"(See WO'875 at internal page 49).

Hence, a POSITA on reading WO'875 would not only be taught that fumarate salt of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol can be used in a composition with pharmaceutically acceptable carrier, as an effective treatment against resistant Mycobacterium strains, but also would be taught the minimum inhibitory concentration of this compound. Therefore, a POSITA working on treating resistant mycobacterium strains, on reading WO'436 and WO'875 would be motivated to use a pharmaceutically acceptable salt, including fumarate salt of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol in a composition.

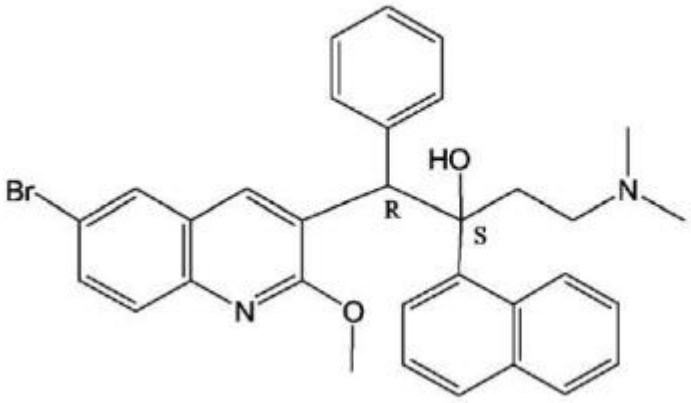
The Opponent relies on the publication WO2006067048 (hereinafter "WO'048" and annexed herein as **Exhibit-C**) titled, "*Quinoline derivatives*

*for the treatment of latent tuberculosis*" in the name of the Applicant of the Present Application. WO'048 was published on 29.06.2006 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO '048 may be relied on as a prior art document.

WO'048 discloses compounds Ia and Ib for treatment of latent tuberculosis. (See WO'048, abstract and internal page 1, lines 4-5). WO'048 discloses that these compounds Ia and Ib are the same as those disclosed in WO'436. WO'048 claims pharmaceutically acceptable salt form of compounds Ia and Ib (See WO'048, internal page 50, claims 1, internal page 55 at claims 21, 23, 24, internal page 56 at claim 27).

WO'048 as well indicates that pharmaceutically acceptable salts of Ia and Ib may include those derived from organic acids such as fumaric acid (See WO'048, internal page 7, lines 4-15). It also discloses that the racemic compounds of either Ia or Ib may be converted into corresponding diastereoisomeric salt forms by reaction with suitable chiral acids (See WO'048, internal page 9, lines 15-20).

Further, WO'048 discloses that compound l-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-l-yl-l-phenyl-butan-2-ol also identified as 6-bromo-α-[2-(dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol is a preferred compound (WO'048, internal page 19, lines 5-17). Further, it discloses that (αS,βR)-6-bromo-α-[2-(dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol and its pharmaceutically acceptable acid addition salt thereof, is also a preferred compound (WO'048, internal page 20, lines 1-5, lines 15-20). The structure of (αS,βR)-6-bromo-α-[2-(dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol is reproduced below for easy reference (WO'048, internal page 20):




Therefore, a POSITA on reading WO'048, WO'875 and WO'436, working on developing a composition for treating mycobacterium infections would be motivated to use a pharmaceutically acceptable form, including a fumaric salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol, a pharmaceutically acceptable carrier and a wetting agent.

**Composition with constituents including lactose monohydrate, hypromellose, polysorbate 20, microcrystalline cellulose, maize starch, colloidal silicon dioxide and magnesium stearate was known**

The Opponent relies on publication no. WO2006024667 (hereinafter "WO'667" and annexed hereto as **Exhibit-D**) filed in name of the Applicant of the Present Application and titled, "fumarate of 4-((4-((4- (2-cyanoethenyl)-2,6-dimethylphenyl)amino)-2-pyrimidinyl)amino)benzonitrile". WO'667 was published on 09.03.2006 viz. much before the priority date of the Present Application viz. 05.12.2006. Thus WO '667 may be relied on as a prior art document.

WO'667 relates to a composition comprising fumarate salt of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (See WO'667, at abstract). WO'667 notes

that, "*Free base 4- [ [4- [ [4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino] -2-pyrimidinyl] -amino]benzonitrile can be classified as a BCS class 2 compound and has thus a low solubility in water. 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile does not only exhibit a low solubility in water, but also in an acidic environment. Consequently, when administered orally in a conventional solid dosage form, a low bioavailability may be expected.*

*When confronted with a BCS class 2 compound intended for oral administration, a person skilled in pharmaceutical technology would turn to exploring possibilities for improving the compound's solubility, for instance by preparing an appropriate salt. This route was also followed for 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzonitrile.*

*The prepared salts appeared to have only a slight improved solubility in water and in HCl. The prepared salts still belong to BCS class 2. Thus, also for the prepared salts a low bioavailability could be expected.*

*Unexpectedly, it has now been found that the fumarate salt (trans CH(COOH)=CH(COOH)) of 4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile, in particular its E-isomer, has a significant improved in vivo bioavailability compared to the free base. In fact, the present salt administered as a solid dosage form has an in vivo bioavailability which is comparable with the bioavailability of the free base administered as an oral PEG 400 solution.*

*Because of the increased bioavailability in vivo, the fumarate salt may be formulated without the need of complex formulation techniques.*

*The fumarate salt of the present invention was also found to be non-hygroscopic and to be chemically and physically stable in different conditions of humidity and temperatures.*" (See WO'667, internal page 2, lines 22-33 and internal page 3, lines 1-19).

Hence, the Applicant of the Present Applicant on previous occasion had found in case of a Biopharmaceutics Classification System (BCS) class 2 drug, the fumarate salt of the free base was found to be more bioavailable. Therefore, there is no inventive step in using a fumarate salt of known compound in a composition, especially in the case of a BCS class 2 compound.

As discussed in the section related to treatment of MDR-TB, it may be noted here that Bedaquiline (the fumarate salt of which is one of the constituents of the claimed composition in Present Application) is also a BCS class 2 drug.

In fact, many portions of the Present Application are verbatim reproduction from WO'667. Particularly, the Present Application has reproduced the portions related to use of a wetting agent in the composition. The same is being reproduced in tabular form below for easy reference:

| **WO2006024667** | **Present Application** |
|---|---|
| [Internal page 11, at lines 34 through internal page 16 at line 08] | [See internal page 7 at line 31 through internal 12 at line 10] |
| '*The pharmaceutical compositions of the present invention preferably comprise a wetting agent.*<br>*As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.*<br><br>*It is well-known in the art that a wetting agent is an amphiphilic compound; it* | "*The pharmaceutical compositions of the present invention preferably comprise a wetting agent.*<br>*As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.*<br><br>*It is well-known in the art that a wetting agent is an amphiphilic compound; it* |

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| *contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.*<br><br>*The terms "hydrophilic" or "hydrophobic" are relative terms.*<br><br>*The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value"). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents.*<br><br>*As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.*<br><br>*The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular* | *contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.*<br><br>*The terms "hydrophilic" or "hydrophobic" are relative terms.*<br><br>*The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic- lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents.*<br><br>*As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.*<br><br>*The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a* |

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| *wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.* | *particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.* |
| *A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.* | *A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.* |
| *The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.* | *The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.* |
| *Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.* | *Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.* |
| *Suitable wetting agents which may be used in the present invention comprise :*<br>*a) Polyethylene glycol fatty acid* | *Suitable wetting agents which may be used in the present invention comprise :*<br>*a) Polyethylene glycol fatty acid* |

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| *monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor, Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)*<br><br>*b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12 dilaurate or distearate or dioleate, PEG-* | *monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-IO laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor,Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)*<br><br>*b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12* |

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| *20 dilaurate or distearate or dioleatePEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco, Cithrol)*<br><br>*c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)*<br><br>*d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,*<br><br>*e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, pentaerythritol and the like with natural* | *dilaurate or distearate or dioleate, PEG-20 dilaurate or distearate or dioleatePEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco,Cithrol)*<br><br>*c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)*<br><br>*d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,*<br><br>*e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol,* |

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| *and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil , PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG- 80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG- 8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearoyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley, Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),* | *pentaerythritol and the like with natural and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil , PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG-8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearoyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley,* |

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| | *Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),* |
| *f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance poly glyceryl- 10 laurate or oleate or stearate, poly glyceryl- 10 mono and dioleate, polyglyceryl polyricinoleate and the like; (the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)* | *f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance polyglyceryl-10 laurate or oleate or stearate, polyglyceryl-10 mono and dioleate, polyglyceryl polyricinoleate and the like;(the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)* |
| *g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)* | *g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)* |
| *h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan monolaurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan* | *h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan mono laurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan* |

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| *monooleate or sorbitan monolaurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)* | *monooleate or sorbitan mono laurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)* |
| *i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)* | *i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)* |
| *j) Sugar esters such as for instance sucrose distearate/monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)* | *j) Sugar esters such as for instance sucrose distearate/ monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)* |

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| *k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 ocyl phenol ether (Triton N series) and the like;* | *k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 ocyl phenol ether (Triton N series) and the like;* |
| *l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)* | *l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)* |
| *m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,* | *m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfo succinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,* |

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| *phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearoyl propylene glycol hydrogen succinate, mono/ diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactylic esters of fatty acids, calcium/sodium stearoyl-2-lactylate, calcium/sodium stearoyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl* | *phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxy ethylene- 10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearoyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono-and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactylic esters of fatty acids, calcium/sodium stearoyl-2-lactylate, calcium/sodium stearoyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl* |

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|---|---|
| *benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.* | *benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.* |
| *When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.* | *When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.* |
| *Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.* | *Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.* |
| *Preferred wetting agents in the present compositions are sodium lauryl sulfate, sodium dioctyl sulfosuccinate, or those wetting agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.* | *Preferred wetting agents in the present compositions are those agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.* |
| *In the compositions of the invention, the* | *In the compositions of the invention, the* |

| | |
|---|---|
| *wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.*<br><br>*The quantity of wetting agent used in the present compositions may depend on the amount of the compound of formula (I), (I-a) or (I-b) present in the composition or on the particle size of the compound of formula (I), (I-a) or (I-b). A higher amount or a smaller particle size may require more wetting agent.*" | *wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.*<br><br>*The quantity of wetting agent used in the present compositions may depend on the amount of the compound present in the composition or on the particle size of the compound. A higher amount or a smaller particle size may require more wetting agent.*" |

In fact, WO'667 claims a composition that has the same composition by weight as claimed in the Present application. As represented below, claim 5 of the Present Application uses the same weight composition as claimed in claim 11 of WO'667.

| **Claim 5 of Present Application** | **Claim 11 of WO '667**<br>(Also see internal page. 19 lines 15-24) |
|---|---|
| Claim 5 " *A pharmaceutical composition according to claim 4 comprising by weight based on the total weight of the tablet core*<br>*(a) from 5 to 50% of active ingredient;*<br>*(b) from 0.01 to 5 % of a wetting* | Claim 11 "*A pharmaceutical composition according any one of claims 4-10 having following composition:*<br>*(a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);(b) from 0.01* |

| | |
|---|---|
| *agent;* | *to 5% of a wetting agent;* |
| *(c) from 40 to 92% of a diluent;* | *(c) from 40 to 92% of a diluent;* |
| *(d) from 0 to 10 % of a polymer;* | *(d) from 0 to 10% of a polymer;* |
| *(e) from 2 to 10 % of a disintegrant;* | *(e) from 2 to 10% of a disintegrant;* |
| *(f) from 0.1 to 5% of a glidant;* | *(f) from 0.1 to 5% of a glidant;* |
| *(g) from 0.1 to 1.5 % of a lubricant."* | *(g) from 0.1 to 1.5% of a lubricant."* |

Further, WO'667 also discloses weight wise distribution of each of the constituents of the composition. These constituents included active ingredient, lactose monohydrate, hypromellose 2910, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate. It discloses that, "'*Tablet compositions illustrating the present invention are:*

*Composition 2a*

*Tablet core*:

*Compound of formula (I-a) 110 mg (i.e. 100 mg base equivalent)*

*Lactose monohydrate 137.8 mg*

*Hypromellose 2910 15mPa.s 5.6 mg*

*Polysorbate 20 1.4 mg*

*Microcrystalline cellulose 52.5 mg*

*Croscarmellose sodium 17.5 mg*

*Colloidal silicon dioxide 1.05 mg*

*Magnesium stearate 2.45 mg*" (See WO'667, internal page 26, and generally internal pages 24-30). WO'667 also gives other examples with different weight of the constituents of the composition. For a POSITA working on developing a composition with similar constituents, varying the weight of the constituents would be a matter of trial and error. Therefore, a POSITA working on developing an anti-mycobacterium treatment using (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-naphthalenyl-β-phenyl-3-quinolineethanol salt on reading WO'667 would be taught to make a composition comprising various constituents such as lactose monohydrate,

polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate to arrive at a composition claimed in claim 7 of the Present Application.

Hence, a POSITA working on developing a composition for treating mycobacterium resistance, on reading WO'667 would be motivated to use fumarate salt of a known substance with anti-mycobacterium activity in a composition with other constituents as used in WO'667.

The Opponent relies on US patent US 6,534, 508 titled, "*Methods and Composition for treating infection using optically pure (S)-Lomefloxacin*" (hereinafter "US'508" and annexed herein as **Exhibit-E**). The patent was published on 23.05.2002, which is earlier than the priority date of the Present Application. Therefore, US'508 may be relied on as prior art.

US'508 relates to composition for treating bacterial infection, in particular, Mycobacteria infection. (See internal page 1, RHS at abstract). It discloses that, "*Usual pharmaceutical media includes, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.*" (See US'508, column 10, lines 5-16)

Further, it cites examples of oral compositions as reproduced below:

Example 1

Oral Formulation

Capsules:

| Formula | Quantity per Capsule in mg. | |
|---|---|---|
| Active Ingredient (S)-lomefloxacin hydrochloride | 100 | 200 |
| Lactose | 349 | 249 |
| Corn Starch | 50 | 50 |
| Magnesium Stearate | 1.0 | 1.0 |
| Compression Weight | 500 | 500 |

(See US'508, column 11)

Example 2

Oral Formulation

Tablets

| Formula | Quantity per Capsule in mg. | |
|---|---|---|
| Active Ingredient (S)-lomefloxacin hydrochloride | 100 | 200 |
| Lactose BP | 309 | 209 |
| Starch BP | 60 | 60 |
| Pregelatinized Maize Starch BP | 30 | 30 |
| Magnesium Stearate | 1 | 1 |
| Compression Weight | 500 | 500 |

Therefore, US'508 discloses oral formulation composition that includes the active ingredient, lactose, corn starch, magnesium stearate. Hence, a POSITA working on developing a composition for treating mycobacteria infection, on reading US'508 would be motivated to include corn starch and magnesium stearate in the composition.

A POSITA, working on developing a composition for treating mycobacterium infection, on reading WO'048, WO'875 and WO'436, WO'667, US'508 would be motivated to use a pharmaceutically acceptable form, including a fumaric salt of (alpha S, beta R)- 6-bromo-α-[2-

(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol along in a composition with excipients taught by prior art documents to arrive at the composition claimed in the Present Application. The constituents of the composition *inter alia* as taught by the prior art could include lactose, maize starch, hyperomellose, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. Such composition in tablet form, as per teachings of the prior art document may also be film coated, as claimed in the Present Application. Therefore, the composition of claims 1-7 of the Present Application are obvious and should be rejected for lack of inventive step.

**THAT CLAIMS 1-7 OF THE PRESENT APPLICATION DO NOT SATISFY THE TEST OF SECTION 3(d) AND SECTION 3(e) AND THEREFORE ARE OBJECTED TO UNDER SECTION 25(1) (f)**

Section 25(1)(f) of the Patents Act allows opposition to grant of patent on the ground of the claimed invention not being an invention within the meaning of the Patents Act, 1970. Section 25(1)(f) reads as follows:

> "*(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground—*
>
> ..
>
> *(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.*"

**Claims of Present Application not an invention under Section 3(d)**

Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims of the Present Application fail under Section 3(d).

Section 3(d) of the Patents Act disallows patents on modification of known substances. It is an established position of law that S. 3(d) has to be satisfied

independently of Section 2(1)(j) and S. 2(1)(ja) [see *Novartis AG versus Union of India and Others* (2013) 6 SCC 1]. The burden of showing enhanced (therapeutic) efficacy of modified known substance, under S. 3(d) is on the Applicant (see *Novartis AG versus Union of India and Others* 2007 4 MLJ 1153, para 13). Further, such data has to be provided by the Applicant in the complete specification (Hon'ble IPAB, *Novartis AG versus Union of India*, MIPR 2009 (2) 0345, para 9(xvii)).

The Applicant again places reliance on WO '436. It is submitted that the publication discloses (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol as one of the compounds that falls within the purview of the claimed formula. This compound is identified as compound 12 (See internal page 34 of WO'436). Further, WO '436 also discloses the $pIC_{50}$ value of compound 12 as 8.7 (See WO'436, Table 5, internal page 46).

The Applicant itself has admitted that (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol, one of the ingredients in the composition claimed by the Applicant, has been already disclosed in WO 2004/011436. The Applicant has failed to show how the composition claimed in the present application shows an enhanced efficacy over the known and disclosed compound in WO'436.

Section 3(d) of the patents act provides that a known substance may include combination of known substances. The claims of the present application are related to a combination of known substances and therefore must fulfil Section 3(d). As submitted above, the applicant has failed to show enhanced efficacy of the claimed compound over the known substance and hence fail to meet the standard laid down under Section 3(d). Hence, the claims of the present application are liable to be rejected under Section 3(d).

Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims of the Present Application fail under Section 3(e).

It is submitted that claims 1-7 of the Present Application are liable to be rejected as the claimed compounds are mere admixtures resulting in mere aggregation of properties and not an invention under Section 3(e) of the Patents Act.

An applicant claiming a combination of compounds is required to show the enhanced additive effect or synergism in the complete specification itself. "*The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.*" (See order of the Asst. Controller of Patents & Designs in patent application no. 314/MUM/2008, at lines 3-5 at internal page 7 and annexed herein as **Exhibit-F**).

Merely providing the composition of each of the ingredients in terms of weight does not discharge the burden of showing synergism. The Asst. Controller of Patents & Designs, while rejecting application no. 3725/CHENP/2006, on grounds of Section 3(e) noted, "*Applicant doesn't provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead examples 1, 2 and 3 provide only the amount of individual components in grams.*" (See the order of the Controller in 327/CHENP/2006, hereto annexed as **Exhibit-G** at internal page 4. Para 8)

It is submitted that composition claimed in Claims 1-7 of the Present Application are mere admixture of known substances resulting in aggregation of properties of the individual components. Therefore, the claimed invention does not overcome S.3(e). Further, the Applicant has failed to disclose any synergistic effect of the claimed composition anywhere in the complete specification. Thus, it is submitted that claims 1-7

of the Present Application are not an invention per Section 3(e) and thus be rejected.

**THAT CLAIMS 1-7 OF THE PRESENT APPLICATION MUST BE REJECTED AS THE COMPLETE SPECIFICATION DOES NOT SUFFICIENTLY AND CLEARLY DESCRIBE THE INVENTION**

Without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(1) (g). It is submitted that the Present Application does not sufficiently and clearly describe the invention claimed.

It is submitted that the Present Application has failed to indicate why only certain weight of the alleged inventive composition has been claimed. The Applicant has failed to provide any reasoning for the amount of constituents of the composition as claimed in claims 3, 5 and 6 of the Present Application.

It is submitted that the Applicant has failed to indicate any advantage of the claimed percentage or specific weight over those broadly disclosed range in the complete specification.

It is further submitted that the Applicant has failed to disclose any advantage or benefit of use of the composition claimed in claims 1-7 of the Present Application.

The Present Application has not discussed the exact problem in prior art WO'436 which had to be overcome by using the composition as claimed in the Present Application. The Applicant has failed to indicate any specific advantage/ merit of the claimed pharmaceutical composition.

**THAT THE APPLICANT HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED BY SECTION 8, AND THEREFORE OBJECTION IS RAISED UNDER S.25(1)(h)**

It is submitted that Section 25(1)(h) allows raising an objection against grant of patent if the applicant has failed to provide information as required under

Section 8 of the Patents Act. Without prejudice to other grounds raised herein, the Present Application should be rejected because the Patent Applicant has not complied with the mandatory requirements of Section 8 of the Patents Act.

It is submitted that the Applicant of the Present Application has not provided detailed particulars of the information required under Section 8. The details of the corresponding national applications vis-à-vis which the information has not been provided by the Applicant are indicated below:

| National Application Number | Information not provided by the Applicant |
|---|---|
| AR064149A1 | Refusal by the patent office was not communicated by the Applicant |
| EP2086940 | Opposition filed at EPO and documents pertaining thereto were not forwarded to the Indian Patent Office. |
| BRPI0719693 | Change in status of the application was not indicated |
| KR10-2009-7011043 | Office action of the KIPO was not filed at the Indian Patent Office |

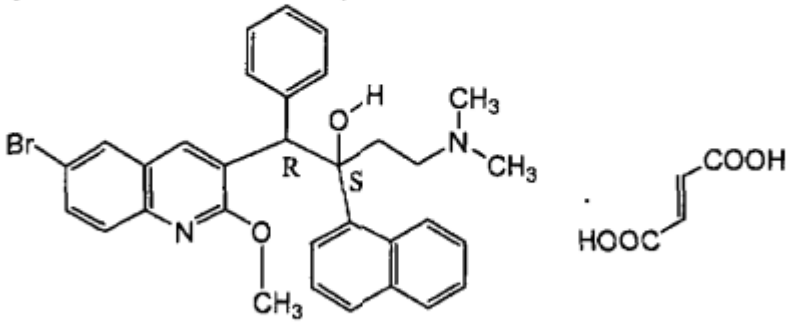
It is submitted that the complete information related to the corresponding applications in other jurisdictions has not been provided by the Applicant. The Opponent therefore, requests the Controller to direct the Applicant to submit translated copies of the opposition proceedings and office actions in these jurisdictions to facilitate examination of the Present Application.

The original filed claims 1-21 are mentioned below;

1. Fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol.

2. (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol (2E)-2-butenedioate (1:1)

3. A compound having the following structure




4. A compound according to any one of claims 1 to 3 for use as a medicine.

5. A compound according to any one of claims 1 to 3 for use as a medicine to treat or prevent a mycobacterial infection.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 3.

7. A pharmaceutical composition according to claim 6 wherein the composition is suitable for oral administration.

8. A pharmaceutical composition according to claim 6 or 7 wherein the composition is a solid composition.

9. A pharmaceutical composition according to any one of claims 6 to 8 further comprising a wetting agent.

10. A pharmaceutical composition according to claim 9 wherein the wetting agent is a polyethylene glycol sorbitan fatty acid ester.

A pharmaceutical composition according to any one of claims 6 to 10 comprising by weight based on the total weight of the composition :

(a) from 5 to 50% of active ingredient;

(b) from 0.01 to 5% of a wetting agent;

(c) from 40 to 92% of a diluent;

(d) from 0.1 to 5% of a glidant.

A pharmaceutical composition according to any one of claims 6 to 11 wherein the composition is in the form of a tablet.

A pharmaceutical composition according to claim 12 comprising by weight based on the total weight of the tablet core

(a) from 5 to 50% of active ingredient;

(b) from 0.01 to 5 % of a wetting agent;

(c) from 40 to 92% of a diluent;

(d) from 0 to 10 % of a polymer;

(e) from 2 to 10 % of a disintegrant;

(f) from 0.1 to 5% of a glidant;

(g) from 0.1 to 1.5 % of a lubricant.

A pharmaceutical composition according to claim 12 or 13 having the following composition

| | |
|---|---|
| Active ingredient | 120.89 mg (i.e. 100 mg base equivalent) |
| Lactose monohydrate (200 mesh) | 152.91 mg |
| Maize starch | 66 mg |
| Hypromellose 2910 15mPa.s | 8 mg |
| Polysorbate 20 | 1 mg |
| Microcrystalline cellulose | 82.2 mg |
| Croscarmellose sodium | 23 mg |
| Colloidal silicon dioxide | 1.4 mg |
| Magnesium stearate | 4.6 mg |

A pharmaceutical composition according to any one of claims 12 to 14 which is film-coated.

16. A process for preparing a pharmaceutical composition according to any one of claims 12 to 15 comprising the following steps :

(i) dry blending the active ingredient and part of the diluent;

(ii) preparing a binder solution by dissolving the binder and the wetting agent in the binder solution solvent;

(iii) spraying the binder solution obtained in step (ii) on the mixture obtained in step (i);

(iv) drying the wet powder obtained in step (iii) followed by sieving and optionally mixing;

(v) mixing the remaining part of the diluent, the disintegrant and the optional glidant in the mixture obtained in step (iv);

(vi) optionally adding the lubricant to the mixture obtained in step (v);

(vii) compressing the mixture obtained in step (vi) into a tablet;

(viii) optionally film-coating the tablet obtained in step (vii).

17. A process for preparing a pharmaceutical composition according to any one of claims 12 to 15 comprising the following steps :

(i) dry blending the active ingredient and part of the diluent;

(ii) preparing a granulation solution optionally containing the binder and wetting agent;

(iii) spraying the granulation solution obtained in step (ii) on the mixture obtained in step (i);

(iv) drying the wet granulate obtained in step (iii) followed by sieving and optionally mixing;

(v) mixing the remaining part of the diluent, the disintegrant, the optional glidant and optionally the binder and wetting agent in the mixture obtained in step (iv);

(vi) optionally adding the lubricant to the mixture obtained in step (v);

(vii) compressing the mixture obtained in step (vi) into a tablet;

(viii) optionally film-coating the tablet obtained in step (vii).

18. Use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment or the prevention of a mycobacterial infection.

19. Use of a compound as claimed in claim 18 for the manufacture of a medicament for the treatment of a mycobacterial infection.

20. Use of a compound as claimed in claim 18 or 19 for the preparation of a medicament for the treatment of a mycobacterial infection wherein the medicament is to be given to a fed subject.

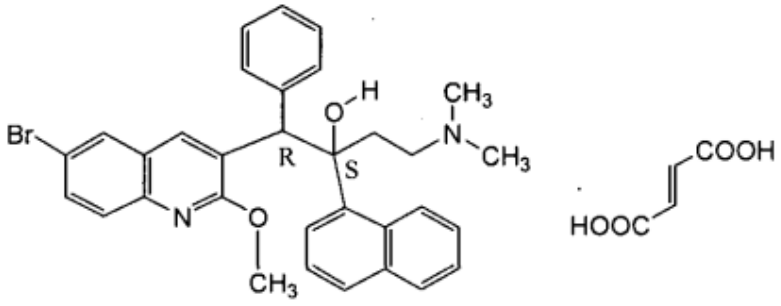
21. Process for the preparation of a compound as claimed in any one of claims 1 to 3 characterized by reacting the corresponding free base with fumaric acid in the presence of a suitable solvent.

7. After filing Form 13 one new claim 22 was added as claims 1-22 for which protection is sought is mentioned below in whose respect objections were raised in the FER.

1. Fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol.

2. (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol (2E)-2-butenedioate (1:1)

3. A compound having the following structure




4. A compound according to any one of claims 1 to 3 for use as a medicine.

5. A compound according to any one of claims 1 to 3 for use as a medicine to treat or prevent a mycobacterial infection.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 3.

7. A pharmaceutical composition according to claim 6 wherein the composition is suitable for oral administration.

8. A pharmaceutical composition according to claim 6 or 7 wherein the composition is a solid composition.

9. A pharmaceutical composition according to any one of claims 6 to 8 further comprising a wetting agent.

10. A pharmaceutical composition according to claim 9 wherein the wetting agent is a polyethylene glycol sorbitan fatty acid ester.

11. A pharmaceutical composition according to any one of claims 6 to 10 comprising by weight based on the total weight of the composition :
(a) from 5 to 50% of active ingredient;
(b) from 0.01 to 5% of a wetting agent;
(c) from 40 to 92% of a diluent;
(d) from 0.1 to 5% of a glidant.

12. A pharmaceutical composition according to any one of claims 6 to 11 wherein the composition is in the form of a tablet.

13. A pharmaceutical composition according to claim 12 comprising by weight based on the total weight of the tablet core
(a) from 5 to 50% of active ingredient;
(b) from 0.01 to 5 % of a wetting agent;
(c) from 40 to 92% of a diluent;
(d) from 0 to 10 % of a polymer;
(e) from 2 to 10 % of a disintegrant;
(f) from 0.1 to 5% of a glidant;
(g) from 0.1 to 1.5 % of a lubricant.

14. A pharmaceutical composition according to claim 12 or 13 having the following composition

| | |
|---|---|
| Active ingredient | 120.89 mg (i.e. 100 mg base equivalent) |
| Lactose monohydrate (200 mesh) | 152.91 mg |
| Maize starch | 66 mg |
| Hypromellose 2910 15mPa.s | 8 mg |
| Polysorbate 20 | 1 mg |
| Microcrystalline cellulose | 82.2 mg |
| Croscarmellose sodium | 23 mg |
| Colloidal silicon dioxide | 1.4 mg |
| Magnesium stearate | 4.6 mg |

15. A pharmaceutical composition according to any one of claims 12 to 14 which is film-coated.

16. A process for preparing a pharmaceutical composition according to any one of claims 12 to 15 comprising the following steps :

(i) dry blending the active ingredient and part of the diluent;

(ii) preparing a binder solution by dissolving the binder and the wetting agent in the binder solution solvent;

(iii) spraying the binder solution obtained in step (ii) on the mixture obtained in step (i);

(iv) drying the wet powder obtained in step (iii) followed by sieving and optionally mixing;

(v) mixing the remaining part of the diluent, the disintegrant and the optional glidant in the mixture obtained in step (iv);

(vi) optionally adding the lubricant to the mixture obtained in step (v);

(vii) compressing the mixture obtained in step (vi) into a tablet;

(viii) optionally film-coating the tablet obtained in step (vii).

17. A process for preparing a pharmaceutical composition according to any one of claims 12 to 15 comprising the following steps :

(i) dry blending the active ingredient and part of the diluent;

(ii) preparing a granulation solution optionally containing the binder and wetting agent;

(iii) spraying the granulation solution obtained in step (ii) on the mixture obtained in step (i);

(iv) drying the wet granulate obtained in step (iii) followed by sieving and optionally mixing;

(v) mixing the remaining part of the diluent, the disintegrant, the optional glidant and optionally the binder and wetting agent in the mixture obtained in step (iv);

(vi) optionally adding the lubricant to the mixture obtained in step (v);

(vii) compressing the mixture obtained in step (vi) into a tablet;

(viii) optionally film-coating the tablet obtained in step (vii).

18. Use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment or the prevention of a mycobacterial infection.

19. Use of a compound as claimed in claim 18 for the manufacture of a medicament for the treatment of a mycobacterial infection.

20. Use of a compound as claimed in claim 18 or 19 for the preparation of a medicament for the treatment of a mycobacterial infection wherein the medicament is to be given to a fed subject.

21. Process for the preparation of a compound as claimed in any one of claims 1 to 3 characterized by reacting the corresponding free base with fumaric acid in the presence of a suitable solvent.

**22. Use of a compound as claimed in any one of claims 18 to 20 wherein the mycobacterial infection is an infection with *Mycobacterium tuberculosis.***

8.

8. The objections raised in FER for compliance by the applicant within prescribed time line are as follows:

**SUB : First Examination Report**

| | | |
|---|---|---|
| APPLICATION NUMBER | : | 1220/MUMNP/2009 |
| DATE OF FILING | : | 29/06/2009 |
| DATE OF REQUEST FOR EXAMINATION | : | 23/04/2010 |
| DATE OF PUBLICATION | : | 14/08/2009 |

a) With reference to the RQ No. 1219/RQ-MUM/2010 Dated 23/04/2010 in the above mentioned application for Grant of Patent , Examination has been conducted under Section 12 and 13 of the Patents Act 1970 , The following objections are hereby communicated.

b) Objections :

1 Form 13 filed for voluntary amending claims at the national phase can not be allowed.Form 13 filed for the amendments of claims by way of addition of claims can not be allowed as per the provisions of sec 59 of the Act. The amendments as per sec 59 can be carried either by way of explanation or correction or disclaimer but cannot be by way of addition of new claims. Further you have not filed a marked copy of the amendments carried out in claims. Therefore, you are required to file a those set of claims which are filed before PCT and on which ISR & IPER is established.

2 Subject matter claimed in claim 1-21 is not fulfilling requirement of section 2 (1) (j) of Patents Act being obvious over 01-03 as cited in International Search Report; for details please refer to Written Opinion of the International Searching Authority;

3 Subject matter claimed in claims 1-5 is not patentable u/s 3 (d) of Patents Act;

4 Subject matter claimed in claims 18-20, 22 is not an invention within meaning of section 2 (1) (j) of Patents Act;

5 Details regarding application for Patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within Six months from the date of filing of the said application under clause(b) of sub section(1) of secton 8 and rule 12(1) of Indian Patent Act.

6 Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent offices along with appropriate translation where applicable, should be submitted within a period of Six months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.

c) You are requested to comply with the objections by filing your reply by way of explanation and/or amendments within 12 months from the date of issue of FER failing which your application will be treated as "Deemed to have been abandoned" under section 21(1) of the Act. The last Date is 12/03/2013.

d) You are advised to file your reply at the earliest so that the office can further proceed with application and complete the process within the prescribed period.

(A T Patre)
Asst. Controller of Patents & Designs

9. Hearing Notice dated 24/08/2022 with the following objections was issued:

**Objections**

**Clarity and Conciseness**

1. The term "suitable" in claim 2 is vague and not clear as it has no limiting effect on the said claim, hence not allowable u/s 10(4)(c) and 10(5) of the Indian Patents Act, 1970 (as amended).

**Formal Requirement(s)**

1. The registration no(s). of all the patent agents authorized by the applicant as per the power of authority submitted to the office, should be provided.

**Invention u/s 2(1)(ja)**

1. D1(WO 2004/011436; Janssen Pharmaceutica N.V.; 2004-02-05) discloses an invention related to novel substituted quinoline derivatives according to formulae Ia and Ib. Enantiomer (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl3-quinolineethanol corresponds to compound 12 (A1 enantiomer) in D1 and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis (see internal page 2 of the complete specification of present application, lines 21-24); ?pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the N-oxide forms thereof of the above disclosed compounds. (abstract at lines 1-3, and claim 1 at internal page 52). D1 also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound. The compounds may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed.

   D2 (WO/2005/117875; Janssen Pharmaceutica N.V.; 2005-12-15) describes fumarate salt of (αS, βR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxyα-1-naphthalenyl-β-phenyl-3-quinolineethanol can be used in a composition with pharmaceutically acceptable carrier, as an effective treatment against resistant Mycobacterium strains, but also would be taught the minimum inhibitory concentration of this compound.

   D3 (WO2006067048; Janssen Pharmaceutica N.V. 2006-06-29; page 50, claims 1, page 55 at claims 21, 23, 24, page 56 at claim 27) describes pharmaceutically acceptable salts of Ia and Ib may include those derived from organic acids such as fumaric acid (page 7, lines 4-15). It also discloses that the racemic compounds of either Ia or Ib may be converted into corresponding diastereoisomeric salt forms by reaction with suitable chiral acids (page 9, lines 15-20). D3 discloses that compound l-(6-bromo-2-methoxy-quinolin3-yl)-4-dimethylamino-2-naphthalen-l-yl-l-phenyl-butan-2-ol also identified as 6-bromo-α-[2-(dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-βphenyl-3-quinolineethanol is a preferred compound (page 19, lines 5-17). Further, it discloses that (αS,βR)-6-bromo-α-[2- (dimethylamino)emyl]-2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol and its pharmaceutically acceptable acid addition salt thereof, is also a preferred compound (page 20, lines 1-5, lines 15-20). The structure of (αS,βR)-6-bromo-α-[2-(dimethylamino)emyl]- 2-methoxy-α-l-naphthalenyl-β-phenyl-3-quinolineethanol is reproduced below for easy reference (page 20).

   D4(WO2006024667 A1; Janssen Pharmaceutica N.V., Tibotec Pharmaceuticals Ltd.; 2006-03-09; ) describes relates to a composition comprising fumarate salt of 4-[[4-[[4-(2- cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (abstract). D4 that, ?Free base 4- [ [4- [ [4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino] - 2-pyrimidinyl] -amino]benzonitrile can be classified as a BCS class 2 compound and has thus a low solubility in water. 4-[[4-[[4-(2- cyanoethenyl)-2,6-dimethylphenyl]amino]-2- pyrimidinyl]amino]benzonitrile does not only exhibit a low solubility in water, but also in an acidic environment. Consequently, when administered orally in a conventional solid dosage form, a low bioavailability may be expected. When confronted with a BCS class 2 compound intended for oral administration, a person skilled in pharmaceutical technology would turn to exploring possibilities for improving the compound's solubility, for instance by preparing an appropriate salt. This route was also followed for 4-[[4- [[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzonitrile. The prepared salts appeared to have only a slight improved solubility in water and in HCl.

pyrimidinyl]amino]benzonitrile. The prepared salts appeared to have only a slight improved solubility in water and in HCl. The prepared salts still belong to BCS class 2. Thus, also for the prepared salts a low bioavailability could be expected. D4 also discloses weight wise distribution of each of the constituents of the composition. These constituents included active ingredient, lactose monohydrate, hypromellose 2910, polysorbate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate

D5 (US20020061894A1; Sepracor Inc ; 2002-05-23) discloses relates to composition for treating bacterial infection, in particular, Mycobacteria infection. (page 1, RHS at abstract). It discloses that, ?Usual pharmaceutical media includes, for





example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets (column 10, lines 5-16).

Claims 1-7 do not involve an inventive step u/s 2(1)(j) and 2(1)(ja) of the Indian Patents Act, 1970 (as amended) over any of the documents D1-D5 in view of common general knowledge.

**Non-Patentability u/s 3**

1. 1. As described in any of the documents D1-D5 the alleged composition of claims 1-7 has been considered to be the same substance as disclosed in the cited prior art in view of section 3(d) of the Act. Hence the said claims are not patentable u/s 3(d) of the Patents Act, 1970(as amended) unless they differ significantly with regard to efficacy compared to the known substance.
   2. Considering documents D1-D5 the alleged composition of claims 1-7 has been considered to be a mere admixture resulting only in the aggregation of the properties of the components thereof. Therefore, the invention as claimed in the said claims is not a patentable invention u/s 3(e) of the Indian Patents Act, 1970 (as amended).

**Other Requirement(s)**

1. With reference to the matter of the application, a hearing u/s 25(1) of the Patent Act , 1970 has been scheduled .You are therefore, required to appear before the Controller for the hearing on the said date and time. You are also requested to prior confirm to the office as well applicant/opponent for attending the same.

2. The alleged claims 1-7 of the instant application appear to conflict with the claim(s) of application no. 220/delnp/2005 (patent no. 236811) with same applicant.

**Sufficiency of Disclosure u/s 10 (4)**

1. 1. Claim 1 is very broad in scope & also does not clearly define the composition as the % or relative proportion of components should be defined clearly & incorporated in claim 1. Also, the term "therapeutically effective amount" in claim 1 are vague and not clear. Such a claim would impose a severe and undue burden on those wishing to ascertain the scope of the claim, hence not allowable u/s 10(4)(c) and 10(5) of the Indian Patents Act, 1970 (as amended). The claim should be restricted to be within the scope of examples disclosed in the specification.
   2. The terms "diluents", "glidant", "polymer", "disintegrant", "lubricant" in claims 3, 5 are very broad and there is no support in the specification that all components within the claimed range will work in thepresent invention, so the limitation of said claims shall be restricted to what is exemplified in examples.

10 After the all the hearings (including hearing held on 17-01-2023 which was offered for the amended claims submitted by the applicant on 14-12-2022) as mentioned above the applicant filed written submission to the hearing with amendment to the claims 1-5 which are as follows:

1. A solid pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient, a therapeutically effective amount of the fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinollineethanol and as a wetting agent, a polyethylene glycol sorbitan fatty acid ester, wherein the composition comprises by weight based on the total weight of the composition:

(a) from 5 to 50% of active ingredient;

(b) from 0.01 to 5% of said wetting agent;

(c) from 40 to 92% of a diluent;

(d) from 0.1 to 5% of a glidant.

2. The pharmaceutical composition as claimed in claim 1 wherein the composition is in the form of a tablet.

3. The pharmaceutical composition as claimed in claim 1 comprising by weight based on the total weight of the tablet core

(a) from 5 to 50% of the active ingredient;

(b) from 0.01 to 5% of a wetting agent;

(c) from 40 to 92% of a diluent;

(d) from 0 to 10% of a polymer;

(e) from 2 to 10% of a disintegrant;

(f) from 0.1 to 5% of a glidant;

(g) from 0.1 to 1.5% of a lubricant.

4. The pharmaceutical composition as claimed in claim 1 or 3 having the following composition:

| | |
|---|---|
| Active ingredient | 120.89 mg (i.e. 100 mg base equivalent) |
| Lactose monohydrate (200 mesh) | 152.91 mg |
| Maize starch | 66 mg |
| Hypromellose 2910 15mPa.s | 8 mg |
| Polysorbate 20 | 1 mg |

| | |
|---|---|
| Microcrystalline cellulose | 82.2 mg |
| Croscarmellose sodium | 23 mg |
| Colloidal silicon dioxide | 1.4 mg |
| Magnesium stearate | 4.6 mg |

5. The pharmaceutical composition as claimed in any of claims 1 to 4 which is film-coated.

11. The hearing submissions (oral arguments during hearing and written submissions after hearing) of both of the Opponents and the Applicant were considered. It is noted that opponents as well as applicant have cited a number of grounds and case law to establish their stand. During the whole discussion in the hearing, some of the points from both sides were thought to be of ~~are~~ irrelevant/superfluous and some are relevant in the matter of the impugned application under pre-grant opposition. As far as the time line and the procedure as defined in the Patent Act is concerned, all parties have utilized their rights for adjournments in the prescribed manner and was acceptable. All the parties have tried to unnecessarily overburden the Controller by citing a variety of case laws, all of which was not found to be relevant for deciding the pre grant opposition. The instant decision is based on the outcome of the invention disclosed in the complete specification and claims, analysis of the relevant documents and case laws, and the arguments made by both of the opponents and the applicant.

12. The opponents 1 & 2 filed their representations with the following grounds of opposition under section 25 (1)(b), (c), (d), (e), (f), and (h) and 25 (1)(b), (e), (f),(g) and (h), respectively. However ground u/s 25 (1)(h) has been withdrawn by Opponent 1 during the hearing.

**I. GROUNDS: NOVELTY ; UNDER SECTION 25(1) (b) and 25(d))**

That the invention so far as claimed in any claim of complete specification has been published before the priority date of the claim (section 25(l)(b))

25(1)(d) that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim

Both of the Opponents 1 and 2 contested the ground of 25(1) (b) however the Opponent 1 only contested the ground of 25(1)(d).

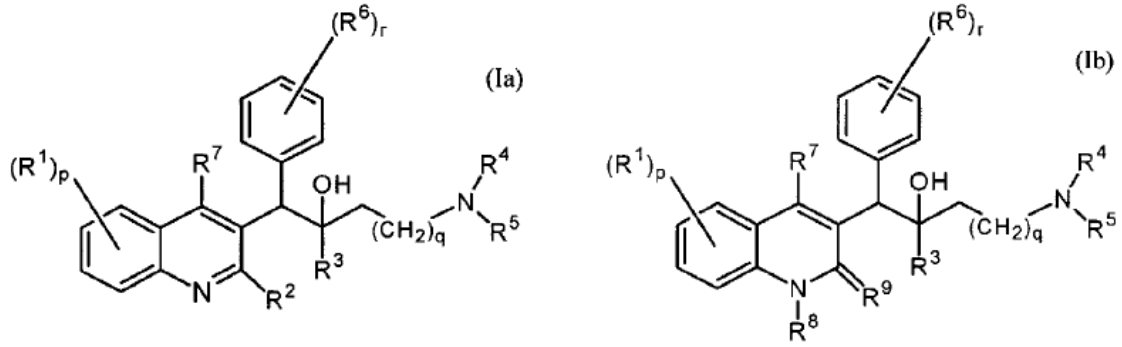
The determination of novelty, for a new invention to be patentable as specified in Section 2 (1)(j) of The Patents Act, 1970, is that the new invention has to be any invention or technology which has not been anticipated by publication in any document or used in the

country or elsewhere in the world before the date of filing of patent application with complete specification, i.e., the subject matter has not fallen in public domain or that it does not form part of the state of the art.

To prove this ground of opposition (Novelty), both the opponents relied on the cited document D1: **WO 2004/011436** only.

After going thoroughly through the complete specification of the impugned application under opposition, it is clear that the application relates to the fumarate salt of (alpha S, beta R)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol) (fumarate salt of Bedaquiline) and its pharmaceutical composition. Particularly amended claim 1 of the present application relates to a solid pharmaceutical composition comprising a pharmaceutically acceptable carrier -as active ingredient, a therapeutically effective amount of the fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-betaphenyl-3-quinollineethanol and as a wetting agent, a polyethylene glycol sorbitan fatty acid ester, wherein the composition comprises by weight based on the total weight of the composition: (a) from 5 to 50% of active ingredient; (b) from 0.01 to 5% of said wetting agent; (c) from 40 to 92% of a diluent; (d) from 0.1 to 5% of a glidant.

D1: WO 2004/011436 discloses a pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) and (Ib) are able to form.




**(57) Abstract:** The present invention relates to novel substituted quinoline derivatives according to the general Formula (Ia) or the general Formula (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof. The claimed compounds are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum*. In particular, compounds are claimed in which, independently from each other, $R^1$ is bromo, p=1, $R^2$ is alkyloxy, $R^3$ is optionally substituted naphthyl or phenyl, q=1, $R^4$ and $R^5$ each independently are hydrogen, methyl or ethyl, $R^6$ is hydrogen, r is equal to 0 or 1 and $R^7$ is hydrogen. Also claimed is a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the claimed compounds, the use of the claimed compounds or compositions for the manufacture of a medicament for the treatment of mycobacterial diseases and a process for preparing the claimed compounds.

The said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydrochloric acid, …; organic acids, for example acetic acid, … **fumaric acid**. The pharmaceutical composition comprising by weight based, depending on the mode of

administration, will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight of active ingredient, and from 1 to 99.95% by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentage being based on the total composition.

D1 discloses the possibility of various salts, in general, it refers for instance to both acid addition salts of a free base and base addition forms of an acid and a fumaric acid is available generally in organic acids list as given below;

The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) and (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid,

maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicyclic acid, p-aminosalicylic acid and pamoic acid.

D1 does not disclose particular pharmaceutical composition of a fumarate salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol) with a wetting agent, polyethylene glycol sorbitan fatty acid ester along with acceptable carrier. Therefore Novelty of the invention has been acknowledged.

Thus, the document D1 cited by the opponent fails to disclose each and every particular feature of the claimed composition ( i.e. the specific fumarate salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3- quinolineethanol); with polyethylene glycol sorbitan fatty acid ester (TWEEN 20 ) as a wetting agent and pharmaceutically acceptable carriers in specific amounts as disclosed in claim 1 of the instant application is not taught in the disclosure of D1) and hence the present invention is clearly novel over the cited document D1. It is I conclude that such a ground of opposition is not validly established by the Opponent 1 & 2.

**II. GROUND: PRIOR CLAIMING ; UNDER SECTION 25(1) (c))**

Opponent 1 made a ground of opposition under Section 25(1)(c) of the Act, that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification

published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

The said opponent submitted that "A novel substituted quinoline compound", being in Patent application No. 220/DELNP/2005 (PCT/EP03/050322) filed on 20.1.2005 which was granted a patent on 23.11.2009 withPatent No. IN236811. However, this application is not related to the prior claiming of the composition particularly fumarate salt of (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3- quinolineethanol); with polyethylene glycol sorbitan fatty acid ester (TWEEN 20 ) as a wetting agent and pharmaceutically acceptable carriers. On account of no record was authenticated during hearing , the opponent 1 failed to establish the alleged ground of opposition.

## III. GROUNDS: OPPOSTION UNDER SECTION 25(1)(e), SECTION 25(1)(f) i.e SECTION 3(d) and (3(e):

Both of the opponents have challenged the impugned application under opposition on the same grounds i.e. (i) that the invention as claimed in any of the claims of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim (under Section 25 (l)(e)); (ii) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or not patentable under this Act (under Section 25(1)(f) i.e. Section 3(d) and 3(e) of the Act

Referring to these grounds, both the opponents cited different documents to establish their claim of lack of inventive step in the invention claimed in the instant application. The documents relied upon by the opponents are already stated as follows:

By the opponent 1:

Exhibit A – Patent No. 236811

Exhibit B – Preparation of Water-soluble compounds through salt formation

Exhibit C - *Remington's Pharmaceutical Sciences* Chapter 89

Exhibit D - EPO 575890 B1 the fumarate salt of a quinoline derivative

Exhibit E - WO 92/10191 quinoline derivatives with pharmaceutical salts, esters, fumarate salts, etc.

Exhibit F - Optical Isomerism in Drugs

Exhibit G - *The Theory and Practice of Industrial Pharmacy* Chapter 11

Exhibit H - *Remington's Pharmaceutical Sciences* Chapter 90

Exhibit I - *The Theory and Practice of Industrial Pharmacy* Chapter 12

Exhibit J – US 5145684 Surface modified drug nano particles

By the opponent 2:

Exhibit A - WO 2004/011436 titled "Quinoline derivatives and their use as mycobacterial inhibitors

Exhibit B - WO2005/117875 titled, "Use of substituted quinoline derivatives for the treatment of drug resistant mycobacterial diseases

Exhibit C - WO2006067048 titled, "Quinoline derivatives for the treatment of latent tuberculosis"

Exhibit D - WO2006024667 titled "Fumarate of 4-((4-((4-(2-cyanoethenyl)-2,6-dimethylphenyl)amino)- 2-pyrimidinyl)amino)benzonitrile"

Exhibit E - US 6,534, 508 titled “Methods and Composition for treating infection using optically pure (S)-Lomefloxacin”

**Documents cited in Hearing Notice;**

D1:WO 2004/011436

D2:WO/2005/117875

D3:WO2006067048

D4:WO2006024667

D5:US20020061894A1

The subject matter of amended claims 1-5 lacks inventive step, as required u/s 2(1)(j) of the Patents Act, 1970 (as amended), statutorily non-patentable u/s 3(d) and u/s 3(e) of the Act .

The following documents which were found most relevant for deciding the patentability of the invention as well as from the view point of the opposition filed which has only been analysed.

**D1: WO 2004/011436**

**Exhibit B is a chapter from a textbook on Medicinal Chemistry, in which the author, Heinrich Stahl; 2003**

**D2: WO2006067048 and D3: WO2006024667**

The originally filed complete specification in page 2 of the specification discloses about the fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1 -naphthalenyl-beta -phenyl-3-quinolineethanol, in particular (alpha S, beta R)-6-bromo-alpha-10 [2-(dimethylaniino)ethyl]-2-methoxy-alpha-l-naphthalenyl-beta-phenyl-3-quinolineethanol (2E)-2-butenedioate (1:1); to pharmaceutical compositions comprising said fumarate salt, to the preparation of the salt and the pharmaceutical compositions.

One of the objective of the instant invention emphasizes that the fumarate salt of (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-l-naphthalenyl-beta-phenyl-3-quinolineethanol is non-hygroscopic and stable. Due to its solubility in water and its dissolution rate, a pharmaceutical composition comprising said salt can be obtained with an acceptable bioavailability.

The specification of the instant invention in the background also discloses 6-bromo-a-[2-(dimethylamino)ethyl]-2-methoxy-a-l--naphthalenyl-P-phenyl-3-quinolineethanol and stereo isomeric forms thereof in D1 as antimycobacterial agents useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as Mycobacterium (M.) tuberculosis, M, bovis, M. avium and M. marinurn.

Enantiomer (alpha S, beta R)-6-bromo-a-[dimethylamino)ethyl]-2-methoxy-CX-l-naphthalenyl-p-phenyl-3-quinolineethanol corresponds to compound 12 (or the Al enantiomer) of D1 and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis is also disclosed.

In Page 4 (line 30) of the specification in the instant case shows that the antimycobacterial activity of the free base is described in WO 2004/011436, which is incorporated herein by reference.

In Page 8 of the specification it is stated that "it is well-known in the art that a wetting agent is an amphiphilic compound; it contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties. The terms "hydrophilic" or "hydrophobic" are relative terms. The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents. As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents".

It is further stated that the present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability. A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention as admitted in the disclosure.

Further, in Pages 9-11, list of suitable wetting agents which may be used in the present invention were also provided. In page 12 of the complete specification it is disclosed that preferred wetting agents in the present compositions are those agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.

Therefore it is clear from the above para's from the complete specification that the object of the present invention is to protect the fumarate salt of Bedaquiline (i.e. alpha S, beta R)-6-bromo-alpha-[2-(mmemylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol) and its pharmaceutical composition for use as a medicine to treat or prevent a mycobacterial infection.

The originally filed fumarate salt of Bedaquiline compound as appeared in claims 1-5 were deleted at the time of reply to FER-. Applicant's agent accepted the view as discussed before in the preceding paragraph that the antimycobacterial activity of the free base is described in D1 well before filing of

the alleged invention. Upon amendment to the claims, the applicant intends to seek protection for particular a pharmaceutical composition of 5 to 50% having fumarate salt of (alpha S, betaR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol with 0.01 to 5% of TWEEN 20 (a polyethylene glycol sorbitan fatty acid ester) as a wetting agent and pharmaceutically acceptable carriers with specific ranges as clamed in amended claim 1. The intention of the applicant to delete the salt of the compound as well as bringing solely a set of claims in the amended stage with a pharmaceutical composition comprising 5 to 50% fumarate salt of bedaquiline (enantiomeric form) with 0.01 to 5% of TWEEN 20 (a polyethylene glycol sorbitan fatty acid ester) as a wetting agent was thoroughly considered vis-à-vis the documents relied upon by the opponents in the pre-grant oppositions filed. However, it is inferred from the written reply of the applicant that to provide enhanced bioavailability, and accordingly to increase dissolution profile rate of the formulation, the presence of 0.01 to 5% of TWEEN 20 as a wetting agent is required and therefore showed an unexpected technical advancement in comparison to the prior art. However, upon analysis of originally filed complete specification it is observed that the applicant failed to disclose any evidence to support the statement made out regarding increase in bio-availability as well as rate of increase in dissolution profile of the composition. To support such fact the applicant's agent submitted the test data in an affidavit dated 22-05-2022 from Sigrid Stokbroekx (one of the inventor) as an afterwards support claiming 159% increase in bioavailability of the drug in its fumarate salt form over the base compound and intrinsic dissolution rate (IDR) of the claimed salt twice as much as the non-salt form of the compound.

Prior art document D1 discloses Enantiomer (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl3-quinolineethanol corresponds to compound 12 (A1 enantiomer) and is a preferred compound to treat mycobacterial diseases, in particular tuberculosis. D1 further discloses the said compound particularly useful in the treatment of Mycobacterium tuberculosis.

D1 further discloses the pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to both Formula (la) and (lb) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (la) and (lb) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, nrnnanoir, acid, lactic acid, nvruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, **fumaric acid**, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicyclic acid, p-aminosalicylic acid and pamoic acid. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the

active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition. The applicant is of the view that the generic disclosure does not bar patenting of a specific composition if such specific composition is not disclosed clearly and unambiguously in the document.

**Exhibit B** filed by opponent 1 is a chapter from a textbook on Medicinal Chemistry, in which the author, Heinrich Stahl, explains the preparation of water-soluble compounds through salt formation. Exhibit B also provides the principles and practical considerations for preparation of salt forms, wherein Table 35.4 it lists the characteristic of base drugs by change of salt form. The same exhibit also teaches that by using the salt form of a drug its solubility increases, and the bioavailability of the drugs also increases (p.73 – Exhibit B). It further lists the fumarate salt as one of the 15 most frequently used acids for salt formation (p. 69 – Exhibit B).

**Further WO2006067048 (D2) also discloses** compounds Ia and Ib for treatment of latent tuberculosis, pharmaceutically acceptable salts of Ia and Ib as mentioned above also that may include those derived from organic acids such as fumaric acid (See D2, page 7, lines 4-15). It also discloses that the racemic compounds of either Ia or Ib may be converted into corresponding diastereoisomeric salt forms by reaction with suitable chiral acids (See D2, 9, lines 15-20).

**Although WO2006024667 (D3) does** not relate to a pharmaceutical composition comprising (alpha S, beta R)- 6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl3-quinolineethanol or its pharmaceutical salts, however, it discloses about commonly used wetting agents.

Many portions of the Present Application are verbatim reproduction from D3, particularly, the portions related to the use of a wetting agent in the composition given as under:

| WO2006024667 | Present Application |
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| [Internal page 11, at lines 34 through internal page 16 at line 08]<br><br>'*The pharmaceutical compositions of the present invention preferably comprise a wetting agent.*<br>*As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.*<br><br>*It is well-known in the art that a wetting agent is an amphiphilic compound; it* | [See internal page 7 at line 31 through internal 12 at line 10]<br><br>"*The pharmaceutical compositions of the present invention preferably comprise a wetting agent.*<br>*As for the wetting agent in the compositions of the invention, there may be used any of the physiologically tolerable wetting agent suitable for use in a pharmaceutical composition.*<br><br>*It is well-known in the art that a wetting agent is an amphiphilic compound; it* |

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| *contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.* | *contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.* |
| *The terms "hydrophilic" or "hydrophobic" are relative terms.* | *The terms "hydrophilic" or "hydrophobic" are relative terms.* |
| *The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value"). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents.* | *The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic- lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents.* |
| *As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.* | *As a rule of thumb, wetting agents having a HLB value greater than about 10 are generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.* |
| *The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular* | *The present compositions preferably comprise a hydrophilic wetting agent. It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a* |

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| *wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.* | *particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability.* |
| *A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.* | *A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present invention.* |
| *The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.* | *The wetting agent of the present invention can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present invention can also be a mixture of two or more wetting agents.* |
| *Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.* | *Suitable wetting agents for use in the compositions of the present invention are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the invention is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.* |
| *Suitable wetting agents which may be used in the present invention comprise :*<br>*a) Polyethylene glycol fatty acid* | *Suitable wetting agents which may be used in the present invention comprise :*<br>*a) Polyethylene glycol fatty acid* |

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| *monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor, Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)*<br><br>*b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12 dilaurate or distearate or dioleate, PEG-* | *monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-IO laurate or oleate or stearate, PEG- 12 laurate or oleate or stearate or ricinoleate, PEG- 15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor,Emulgante, Nikkol, Myrj, Crodet, Albunol, Lactomul)*<br><br>*b) Polyethylene glycol fatty acid diesters comprising diesters of lauric acid, stearic acid, palmic acid, oleic acid and the like with PEG-8, 10, 12, 20, 32, 400 and the like, for instance PEG-8 dilaurate or distearate, PEG-10 dipalmitate, PEG- 12* |

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| *20 dilaurate or distearate or dioleatePEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco, Cithrol)*<br><br>*c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)*<br><br>*d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,*<br><br>*e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, pentaerythritol and the like with natural* | *dilaurate or distearate or dioleate, PEG-20 dilaurate or distearate or dioleatePEG-32 dilaurate or distearate or dioleate, PEG-400 dioleate or distearate; (the wetting agents belonging to this group are for instance known as Mapeg, Polyalso, Kessco,Cithrol)*<br><br>*c) Polyethylene glycol fatty acid mono- and diester mixtures such as for example PEG 4-150 mono and dilaurate, PEG 4-150 mono and dioleate, PEG 4-150 mono and distearate and the like; (the wetting agents belonging to this group are for instance known as Kessco)*<br><br>*d) Polyethylene glycol glycerol fatty acid esters such as for instance PEG-20 glyceryl laurate or glyceryl stearate or glyceryl oleate, PEG-30 glyceryl laurate or glyceryl oleate, PEG- 15 glyceryl laurate, PEG-40 glyceryl laurate and the like; (the wetting agents belonging to this group are for instance known as Tagat, Glycerox L, Capmul) ,*<br><br>*e) Alcohol-oil transesterification products comprising esters of alcohols or polyalcohols such as glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol,* |

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| *and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil , PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG- 80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG- 8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearoyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley, Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),* | *pentaerythritol and the like with natural and/or hydrogenated oils or oil-soluble vitamins such as castor oil, hydrogenated castor oil, vitamin A, vitamin D, vitamin E, vitamin K, an edible vegetable oil e.g. corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, almond oil and the like, such as PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-23 castor oil , PEG-25 hydrogenated castor oil or trioleate, PEG-35 castor oil, PEG-30 castor oil or hydrogenated castor oil, PEG-38 castor oil, PEG-40 castor oil or hydrogenated castor oil or palm kernel oil, PEG-45 hydrogenated castor oil, PEG-50 castor oil or hydrogenated castor oil, PEG-56 castor oil, PEG-60 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides, PEG-80 hydrogenated castor oil, PEG-100 castor oil or hydrogenated castor oil, PEG-200 castor oil, PEG-8 caprylic/capric glycerides, PEG-6 caprylic/capric glycerides, lauroyl macrogol-32 glyceride, stearoyl macrogol glyceride, tocopheryl PEG-1000 succinate (TPGS); (the wetting agents belonging to this group are for instance known as Emalex, Cremophor, Emulgante, Eumulgin, Nikkol, Thornley,* |

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| | *Simulsol, Cerex, Crovol, Labrasol, Softigen, Gelucire, Vitamin E TPGS),* |
| *f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance poly glyceryl- 10 laurate or oleate or stearate, poly glyceryl- 10 mono and dioleate, polyglyceryl polyricinoleate and the like; (the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)* | *f) polyglycerized fatty acids comprising polyglycerol esters of fatty acids such as for instance polyglyceryl-10 laurate or oleate or stearate, polyglyceryl-10 mono and dioleate, polyglyceryl polyricinoleate and the like;(the wetting agents belonging to this group are for instance known as Nikkol Decaglyn, Caprol or Polymuls)* |
| *g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)* | *g) Sterol derivatives comprising polyethylene glycol derivatives of sterol such as PEG-24 cholesterol ether, PEG-30 cholestanol, PEG-25 phyto sterol, PEG-30 soya sterol and the like; (the wetting agents belonging to this group are for instance known as Solulan™ or Nikkol BPSH)* |
| *h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan monolaurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan* | *h) Polyethylene glycol sorbitan fatty acid esters such as for example PEG-10 sorbitan laurate, PEG-20 sorbitan mono laurate or sorbitan tristearate or sorbitan monooleate or sorbitan trioleate or sorbitan monoisostearate or sorbitan monopalmiate or sorbitan monostearate, PEG-4 sorbitan mono laurate, PEG-5 sorbitan monooleate, PEG-6 sorbitan* |

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| *monooleate or sorbitan monolaurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)* | *monooleate or sorbitan mono laurate or sorbitan monostearate, PEG-8 sorbitan monostearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan oleate or sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-80 sorbitan monolaurate, PEG sorbitol hexaoleate (Atlas G- 1086) and the like; (the wetting agents belonging to this group are for instance known as Liposorb, Tween, Dacol MSS, Nikkol, Emalex, Atlas)* |
| *i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)* | *i) Polyethylene glycol alkyl ethers such as for instance PEG-10 oleyl ether or cetyl ether or stearyl ether, PEG-20 oleyl ether or cetyl ether or stearyl ether, PEG-9 lauryl ether, PEG-23 lauryl ether (laureth-23), PEG-100 stearyl ether and the like; (the wetting agents belonging to this group are for instance known as Volpo, Brij)* |
| *j) Sugar esters such as for instance sucrose distearate/monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)* | *j) Sugar esters such as for instance sucrose distearate/ monostearate, sucrose monostearate or monopalmitate or monolaurate and the like; (the wetting agents belonging to this group are for instance known as Sucro ester, Crodesta, Saccharose monolaurate)* |

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| *k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 ocyl phenol ether (Triton N series) and the like;* | *k) Polyethylene glycol alkyl phenols such as for instance PEG- 10- 100 nonyl phenol (Triton X series), PEG- 15- 100 ocyl phenol ether (Triton N series) and the like;* |
| *l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)* | *l) Polyoxyethylene-polyoxypropylene block copolymers (poloxamers) such as for instance poloxamer 108, poloxamer 188, poloxamer 237, poloxamer 288 and the like; (the wetting agents belonging to this group are for instance known as Synperonic PE, Pluronic, Emkalyx, Lutrol™, Supronic, Monolan, Pluracare, Plurodac)* |
| *m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,* | *m) ionic wetting agents including cationic, anionic and zwitterionic surfactans such as the fatty acid salts e.g. sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfo succinate, sodium myristate, sodium palmitate, sodium state, sodium ricinoleate and the like; such as bile salts e.g. sodium cholate, sodium taurocholate, sodium glycocholate and the like; such as phospholipids e.g. egg/soy lecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl glycerol,* |

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| *phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearoyl propylene glycol hydrogen succinate, mono/ diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactylic esters of fatty acids, calcium/sodium stearoyl-2-lactylate, calcium/sodium stearoyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl* | *phosphatidyl serine and the like; such as phosphoric acid esters e.g. diethanolammonium polyoxy ethylene- 10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride; such as carboxylates e.g. succinylated monoglycerides, sodium stearyl fumarate, stearoyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono-and diglycerides, citric acid esters of mono-and diglycerides, glyceryl- lacto esters of fatty acids, lactylic esters of fatty acids, calcium/sodium stearoyl-2-lactylate, calcium/sodium stearoyl lactylate, alginate salts, propylene glycol alginate, ether carboxylates and the like; such as sulfates and sulfonates e.g. ethoxylated alkyl sulfates, alkyl benzene sulfates, alpha-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinate disodium, disodium undecyleneamido-MEA-sulfosuccinate and the like; such as cationic wetting agents e.g. hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl* |

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| *benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.* | *benzylammonium salts, alkylpyridinium salts, betaines (lauryl betaine), ethoxylated amines (polyoxyethylene-15 coconut amine) and the like.* |
| *When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.* | *When in the above list of suitable wetting agents, different possibilities are listed such as for example PEG-20 oleyl ether or cetyl ether or stearyl ether, this means that PEG-20 oleyl ether and PEG-20 cetyl ether and PEG-20 stearyl ether are intended.* |
| *Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.* | *Thus for instance PEG-20 castor oil or hydrogenated castor oil or corn glycerides or almond glycerides has to be read as PEG-20 castor oil and PEG-20 hydrogenated castor oil and PEG-20 corn glycerides and PEG-20 almond glycerides.* |
| *Preferred wetting agents in the present compositions are sodium lauryl sulfate, sodium dioctyl sulfosuccinate, or those wetting agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.* | *Preferred wetting agents in the present compositions are those agents belonging to the group of the polyethylene glycol sorbitan fatty acid esters, such as wetting agents known as Tween, e.g. Tween 20, 60, 80. Most preferred, the wetting agent is Tween 20.* |
| *In the compositions of the invention, the* | *In the compositions of the invention, the* |

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| *wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.*<br><br>*The quantity of wetting agent used in the present compositions may depend on the amount of the compound of formula (I), (I-a) or (I-b) present in the composition or on the particle size of the compound of formula (I), (I-a) or (I-b). A higher amount or a smaller particle size may require more wetting agent."* | *wetting agent is preferably present at a concentration from about 0.01 to about 5% by weight relative to the total weight of the composition, preferably from about 0.1 to about 3 % by weight, more preferably from about 0.1 to about 1 % by weight.*<br><br>*The quantity of wetting agent used in the present compositions may depend on the amount of the compound present in the composition or on the particle size of the compound. A higher amount or a smaller particle size may require more wetting agent."* |

D4 claims a composition that has the same weight ranges of the wetting agent as claimed in the instant application. Claim 5 of the instant application uses the same weight composition of wetting agents and other ingredients as claimed in claim 11 of D3 also.

| Claim 5 of Present Application | Claim 11 of WO '667<br>(Also see internal page. 19 lines 15-24) |
|---|---|
| Claim 5 " *A pharmaceutical composition according to claim 4 comprising by weight based on the total weight of the tablet core*<br>*(a) from 5 to 50% of active ingredient;*<br>*(b) from 0.01 to 5 % of a wetting* | Claim 11 "*A pharmaceutical composition according any one of claims 4-10 having following composition:*<br>*(a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);(b) from 0.01* |
| *agent;*<br>*(c) from 40 to 92% of a diluent;*<br>*(d) from 0 to 10 % of a polymer;*<br>*(e) from 2 to 10 % of a disintegrant;*<br>*(f) from 0.1 to 5% of a glidant;*<br>*(g) from 0.1 to 1.5 % of a lubricant."* | *to 5% of a wetting agent;*<br>*(c) from 40 to 92% of a diluent;*<br>*(d) from 0 to 10% of a polymer;*<br>*(e) from 2 to 10% of a disintegrant;*<br>*(f) from 0.1 to 5% of a glidant;*<br>*(g) from 0.1 to 1.5% of a lubricant."* |

Upon considering the submission from both sides as well as from the disclosure in various prior art, the followings are the observation on considering whether the invention claimed in any claim of the complete specification is inventive or not.

The disclosure of the invention by the applicant in the instant invention, the disclosure and teachings in the prior art D1 or D2, Exhibit B as well as D3, the affidavit filed by the inventor as well as the argument during hearing has been elaborated in the preceding paragraphs. In crux, D1 discloses the base compound along with the suggestion that fumarate salt of Bedaquiline may be feasible in another embodiment, Exhibit B discloses about the salt form of the base compound in the pharmaceutical field in general and the advantage of the salt form over the base compound in terms of the bioavailability; D3 elaborates especially about the use of TWEEN 20 (a polyethylene glycol sorbitan fatty acid ester) as wetting agent in pharmaceutical compositions in the range of 0.01 to 5.0%

The evidence filed in form of affidavit is thought to be supporting the composition claiming a fumarate salt of Bedaquiline and the wetting agent TWEEN 20 as essence of the invention which was not elaborated in details with supporting facts. It was filed only after the objections were emerged. Had it been the only problem to be solved, all such findings could have been well documented and incorporated before the priority date of the application. There is no data has been shown in the

complete specification to show that combination of fumarate salt of Bedaquiline along with Tween 20 would show surprising effect over the known the composition of Bedaquiline on the treatment of a patient. The applicant has failed to have such records and therefore, combining the teachings and suggestions of the prior art Exhibit B and D3, especially with reference to the disclosure in D1, it is obvious to a person skilled in the art to perform the invention. **Therefore, no inventive step can be acknowledged to the set of claims 1-5 claimed in the instant application.**

As far as the invention claimed in any of the claims falls under Section 25(1)(f) of the Act i.e. whether a patentable invention U/S 3(d) and 3(e) of the Act, the analysis is as under:

(b) An invention, especially pharmaceutical product to be patentable it must have to satisfy the criteria as required U/S 3(d) of the Act which is;

*"the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. "*

*"Explanation. -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;"*

In the instant case, the applicant sought protection of a fumarate salt of Bedaquiline which was dropped from the claim during the amended stage. The applicant further emphasized seeking protection for a composition in original claim 6.

In general the salt form of the base compound is the invention and justifying addition of a wetting agent by the applicant at a later stage as the main theme of the invention may not arise. Therefore, the fumarate salt of (alpha S, betaR)-6-bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-1-napthalenyl-β-phenyl-3-quinolineethanol to be patentable should be showing enhanced efficacy and that to unexpected enhanced therapeutic efficacy in comparison with prior art base compound particularly D1 for treatment of Mycobacterium tuberculosis. The comparative data, which has been placed on record, relates to some bioavailability aspect only which can't be correlated with the enhanced therapeutic effect unless data relating to the efficacy of base compound and TWEEN 20 is given (i.e. comparative data of (Bedaquiline + TWEEN 20) and (fumarate salt of Bedaquiline + TWEEN 20). There is no comparative data in the complete specification to show that combination of fumarate salt

of Bedaquiline along with Tween 20 would show significant enhancement of the known efficacy or improved therapeutic efficacy over the known efficacy of the composition of Bedaquiline on the treatment of a patient.

However, it is apparent that the complete specification has failed to disclose an improved therapeutic efficacy over the prior art, and also affidavit is silent regarding improved efficacy, but deposed increase in bio-availability by changes made in use of 0.01 to 5% of wetting agent, which could not lead to an improved efficacy, this can be practiced by changing in the dosages to make increase in bio-availability

As the improved bioavailability would not constitute enhancement in therapeutic efficacy of the pharmaceutical composition unless it shows significant enhancement in known therapeutic efficacy in terms of efficacy results.
In the absence of any such credible evidence regarding enhanced therapeutic effect of the formulation by the use of specific concentration of wetting agent i.e. a polyethylene glycol sorbitan fatty acid ester and carriers such as diluents, glidant , disintegrant; a lubricant, polymer is not justified Further, Annexure A (test data in affidavit from Sigrid Stokbroekx), applicant's agent mentions that the unexpectedly improved bioavailability makes it possible to develop a solid dosage form. Further, it is submitted by the applicant's agent that bioavailability of the solid fumarate salt formulation relative to the solution of the base was found to be 159%.

In this regard, the pharmaceutical composition of base compound Bedaquiline against M. tuberculosis is already covered under the patents previously granted in favour of applicant. Applicant has to show data on how an increase in bioavailability results in increased therapeutic efficacy. The combination of fumarate salt of Bedaquiline along with common pharmaceutically acceptable excipients wetting agent i.e. a polyethylene glycol sorbitan fatty acid ester is considered as known substance and not patentable u/s 3(d) of the Act.

Apart from the above, in the absence of any credible evidence showing the synergistic effect of the claimed formulation, the subject matter as claimed is considered as a mere admixture resulting only in the aggregation of the properties of the components thereof. Therefore, the subject matter as claimed is considered non-patentable u/s 3 (e) of the Act.
Thus, The present application does not meet the requirements of sections 2(1)(j), 3(d) and 3(e) in conjunction.
Therefore, the grounds of obviousness/lack of inventive step (corresponds to section 25(1)(e) of the Act) and non-patentability u/s 3(d) & 3(e) of the Act (corresponds to section 25(1)(f)) the Act are established by the opponents.

## IV. GROUND : INSUFFICIENCY UNDER SECTION 25(1) (g);

**Section 25(1)(g) states that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed**

Opponent 2 has challenged the impugned application under opposition on the same ground, i.e. Under Section 25(1)(g) of The Patents Act, 1970 i.e. the impugned application under opposition does not sufficiently and fairly describe the invention in a manner so as to enable a person skilled in the art to perform or work the invention.

In this regard, the complete specification meets the statutory requirement as mandated under Section 10(4) of The Patents Act, 1970 and that the person skilled in the art would be sufficiently enabled to work on the claimed invention without undue experimentation by simply relying on the disclosure made in the complete specification. The question of insufficiency of disclosure does not arise even if a single working example for performing the invention is disclosed in the complete specification and the law is clear in this regard.

In the present case, the complete specification is supported with working example which sufficiently describes the invention and the manner in which it is to be performed.

Thus, it is my considered view, that the present application under opposition sufficiently and fairly describe the invention in a manner so as to enable an ordinary person skilled in the art to perform or work the invention and is therefore not leading to any insufficiency of disclosure and also does not violate any provisions of Section 10(4) of the Patents Act, 1970.

***I conclude that this ground of opposition is not validly established by Opponent 2.***

## V. GROUND: SECTION 25(1) (h) of The Patents Act

**THAT THE APPLICANT HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED BY SECTION 8, AND THEREFORE OBJECTION IS RAISED UNDER S.25 (1)(h)**

**Opponent 2 submitted that** Applicant of the Present Application has not provided detailed particulars of the information required under Section 8. The details of the corresponding national applications vis-à-vis which the information has not been provided by the Applicant are indicated below:

| National Application Number | Information not provided by the Applicant |
|---|---|
| AR064149A1 | Refusal by the patent office was not communicated by the Applicant |
| EP2086940 | Opposition filed at EPO and documents pertaining thereto were not forwarded to the Indian Patent Office. |
| BRPI0719693 | Change in status of the application was not indicated |
| KR10-2009-7011043 | Office action of the KIPO was not filed at the Indian Patent Office |

In this regard applicant's agent submitted updated Form-3 to the Patent Office with current status of corresponding applications along with petition under rule 137 for condoning the irregularity of the procedure envisaged by Section 8. This has been taken on record and the said objection does not withstand.

13. The instant application does not meet the requirements of section 2(1)(ja) and sections 3(d) & 3(e) of the Patents Act based on the findings from the investigation as well as from the matter presented by the opponents in the pre-grant opposition proceedings as discussed above. Therefore, it is hereby ordered that the invention disclosed and claimed in the instant application 1220/MUMNP/2009 entitled "FUMARATE SALT OF (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO)-ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL" has been refused to proceed further under section 15 of the Act and simultaneously, I dispose both of the pre-grant oppositions as per the provision under Section 25(1) of the Act and corresponding Rules made thereunder.

Dated this 23-03-2023

(Dr. (Miss) Latika Dawara)
Asst. Controller of Patents & Designs
Patent Office Mumbai