BEFORE THE CONTROLLER OF PATENTS
Patent Office, Chennai

In the matter of Patent Application No. 10027/CHENP/2012 filed by M/s ASTELLAS DEUTSCHLAND GMBH

And

In the matter of section 15 of the Act.

DECISION

1. M/s ASTELLAS DEUTSCHLAND GMBH has filed a National Phase Application for patent hereinafter referred as 'applicant' for their invention titled " ORAL DOSAGE FORMS OF BENDAMUSTINE AND THERAPEUTIC USE THEREOF " on 29/11/2012 through their Attorney M/s De Penning and De Penning and it was numbered as 10027/CHENP/2012 for the International Application Number PCT/EP2011/002763 filed on 01/06/2011.
2. The Indian National Phase Patent Application was filed with 29 claims which are related to "A pharmaceutical composition comprising Bendamustine for oral administration."

    1. A pharmaceutical composition for oral administration which comprises bendamustine or a pharmaceutically acceptable, ester, salt or solvate thereof as an active ingredient, and a pharmaceutically acceptable excipient and which shows a dissolution of the bendamustine of at least 60% in 20 minutes, 70% in 40 minutes and 80% in 60 minutes, as measured with a paddle apparatus at 50 rpm according to the European Pharmacopoeia in 500 ml of a dissolution medium at a pH of 1.5, and wherein the pharmaceutically acceptable excipient is either a pharmaceutically acceptable non-ionic surfactant, selected from the group consisting of a polyethoxylated castor oil or derivative thereof and a block copolymer of ethylene oxide and propylene oxide or a pharmaceutically acceptable saccharide selected from the group consisting of one or more of a monosaccharide, a disaccharide, an oligosaccharide, a cyclic oligosaccharide, a polysaccharide and a saccharide alcohol, wherein the ratïo by weight of the active ingredient to the saccharide excipient(s) is in the range of 1:1-5.

3. In response to first examination report, 29 claims have been amended to 13 claims and after hearing amended into 6 claims. Claim1

    1. *A pharmaceutical composition in an oral dosage form of a hard gelatine capsule which comprises bendamustine or a pharmaceutically acceptable salt thereof as an active ingredient, and a pharmaceutically acceptable excipient, wherein the pharmaceutically acceptable excipient is selected from the group consisting of macrogol glycerol hydroxystearate, polyoxyl- 35- castor oil and ethylene oxide/propylene oxide block copolymer wherein it comprises 10 to 1000 mg of the active ingredient; and the relative content of the excipient is 80 to 91%.*

Inventive step:

4. The agent for the applicant submitted that claims have been amended within the scope of the original claims and specification and the oral dosage form of claim 1 has been restricted to 'hard gelatine capsule' (support throughout the description and examples - specifically example 2- page 34 line 13). The pharmaceutically acceptable excipient of claim 1 has been limited only to surfactants such as macrogol glycerol hydroxystearate, polyoxyl- 35- castor oil and ethylene oxide/propylene oxide block copolymer. Saccharide is removed from the list of excipients. Macrogol glycerol hydroxystearate is a a polyethoxylated castor oil, supported by the examples and original claim 1 as filed. Further the amount of bendamustine has been specified, based on previous claim 3, and the relative amount of the excipient is specified, based on majority of the relevant examples as explained hereinafter.

    The agent for the applicant further submitted that the amended claims on file are inventive over the documents cited and the claimed subject matter would not have been obvious to a person skilled in the art from US2006128777 (D1), WO2006076620 (D2) to WO2010063476 (D3). There existed a problem in the art that the oral bendamustine compositions, of the prior art had relatively poor bioavailability results and a large inter-individual variability. In view of the stability problems with the intravenous marketed formulation, once reconstituted with water, and in order to improve the patient compliance there has been a long-felt need for a stable dosage-form comprising bendamustine which is easy to administer to the patient and which provides good bioavailability without large inter- and intra-individual variability. There is also a need for a pharmaceutical composition from which the bendamustine is absorbed completely or at least to a high extend in the stomach, thereby avoiding or reducing the degradation of the bendamustine in the small or large intestine (see the instant specification page 3; paragraph 1).

The agent further submitted as advantages of the present invention, pharmaceutical compositions show a high dissolution *in vitro* reducing the degradation of bendamustine *in vivo*, thus resulting in an improved bioavailability of the bendamustine *in vivo*. The invention shows the preferred fast dissolution profile of bendamustine, which is at least 60 % in 10 minutes, 70% in 20 minutes and 80 % in 30 minutes, as measured with a paddle apparatus at 50 rpm according to the European Pharmacopoeia in 500 ml of an artificial gastric fluid". The composition as in Table 8 and the results of Table 9 to 10 are tabulated below for easy reference.

Example 4	Excipient	Relative Amount of	Dissolution in 30 minutes (%)
4.1	Cremophor RH40	90.8	93.8
4.2	Pluronic L44	88.2	96.7
4.3	Cremophor EL /Gelucire	80.7	104.5
4.4	Pluronic L44 /Gelucire	90.2	109.5
4.5	Cremophor EL	90.8	88.9
4.6	Pluronic L44	90.8	95.0
4.7	Cremophor EL	88.4	72.4

Accordingly, applicant believes that other embodiments according to Claim 1 also provide a fast dissolution and so the desired result with the advantages previously described. Thus the claimed compositions provide surprising effects and these could not have been predicted from D1 to D3.

D1 is not a document which is primarily concerned with the formulation of bendamustine, let alone oral dosage forms of bendamustine. Current protocols for bendamustine treatment are described in paragraph [0047] in D1 and these relate to intravenous, not oral, administration. The only formulation described in D1 is for intravenous, not oral, administration (see paragraph [0123] on page 14 of D1 and paragraph [0132] in D1). There is, furthermore, no motivation from D1 to arrive at the claimed oral dosage composition with the specific surfactants and saccharides (in the defined ratios of bendamustine) in order to produce a composition with good dissolution and stability. D1 does not recognise that the claimed composition would be suitable to deliver bendamustine effectively by oral administration and this is only shown by the present application.

D2 disclosed lyophilized formulations for intravenous administration is essential for bendamustine but not oral, administration (see page 15, lines 8 to 23 in D2).

D3 does not mention bendamustine or any formulation suitable for an oral dosage form comprising bendamustine. There is, therefore, no guiding principle from D3 as to what agents would be suitable for bendamustine to solve the problem of improving dissolution and stability. There is no general teaching in D3 of what excipient would be suitable for a non-exemplified compound. D3 only provides details of excipients for known commercially available formulations but does not presume to provide categorical guidance for compounds not mentioned. There is no pointer from D3 to the claimed oral dosage form comprising bendamustine. Further the present invention recognizes that specific surfactants are required to provide the advantages of the invention as well as specific saccharides. D1 to D3 do not point the skilled person to the excipients which are suitable to provide the advantages of the invention and so the claimed subject matter would not have been obvious from D1 to D3 and is inventive over the cited prior art.

5. D1disclosed bendamustine compositions may also be prepared in a solid form (including granules, powders or suppositories). The compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert excipient such as sucrose, lactose, or starch. Such dosage forms may also comprise additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. D2 disclosed lyophilized bendamustine composition.
   D3 disclosed a pharmaceutical composition in a solid dosage form suitable for oral administration, the composition comprising bendamustine or pharmaceutically acceptable ester, salts or solvates thereof as an active ingredient and at least one pharmaceutically acceptable excipient which is a pharmaceutically acceptable saccharide selected from the group consisting of one or more of a monosaccharide, a disaccharide, an oligosaccharide, a cyclic oligosaccharide, a polysaccharide and a saccharide alcohol, wherein the ratio by weight of the active ingredient to the saccharide excipient(s) is in the range of 1 :2-5 and which composition shows a dissolution of the bendamustine of at least 60% in 20 minutes, 70% in 40 minutes and 80% in 60 minutes as measured with a paddle apparatus at 50 rpm according to the European Pharmacopoeia in 500 ml of a dissolution medium at a pH of 1.5.

The object of the claimed invention is to provide a stable dosage-form comprising bendamustine which is easy to administer to the patient with good bioavailability and absorbed completely or at least to a high extend in the stomach, thereby avoiding or reducing the degradation of the bendamustine in the small or large intestine. For identical object D3 provided a stable oral dosage-form comprising bendamustine which is easy to administer to the patient and provides an increased bioavailability with less variability as compared to the known oral dosage-form.

To improve the dissolution rate of the oral dosage forms the applicant selected the ratio by weight of the bendamustineto the saccharide excipient in the range 1:1-5 which exhibits dissolution of the bendamustine of at least 75 % in 10 minutes, 85% in 20 minutes and 90 % in 30 minutes, as measured with a paddle apparatus at 50 rpm according to the European Pharmacopoeia in an artificial gastric fluid. The excipient required for fast dissolution is saccharide in a ratio with bendamustine is 1:2:5 which are already been identically disclosed in D3. The excipient saccharide responsible for the fast dissolution, ratio of the exipient with bendamustine, dissolution rate and the strength of the active ingredient in the dosage form 10mg to 1000mg are disclosed in D3.

D1 disclosed the solid dosage form of bendamustine with several possible excipients, D3 disclosed all the inventive features of the claimed invention including the strength of the active ingredient and saccharide responsible for fast dissolution with identical proportion. The amended claim 1 cannot be considered as inventive even though certain exicipents are incorporated therein to overcome disclosure in the prior art document D3. The technical effect of the present invention is fast dissolution using saccharide as a excipient which is already disclosed in D3. In the absence of any technical advancement the claimed invention do not involve an inventive step in view of D1 and D3.

<u>Not an invention</u>

6. The applicant submitted that the claimed compositions are not a mere admixture as the excipient modifies the bioavailability and stability of bendamustine and the composition thus exhibits synergistic effect as confirmed by the data in the examples and Figures 1 to 3 as elaborated above. Therefore the claims are outside the ambit of Section 3(e) of the Act.
7. The composition claimed in claim 1 (amended claim) is considered as mere admixture as there is no improved effect or unforeseen effect than the prior art is shown in the complete specification. Thus claims of the claimed invention are not an invention u/s 3(e) of the Act.

8. In view of the discussion in the preceding paragraphs, considering the relevant oral submissions made by the agent for the applicant and all the circumstances of the case, refusing the grant of patent under section 15 of the Act without any order as to costs.

Dated this 26th day of June, 2020.

(Dr.S.P.SUBRAMANIYAN)

Deputy Controller of Patents & Designs