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Datasheet for the decision of 10 September 2007

Case Number: W 0012/06 - 3.3.02

Application Number: PCT/US 2005/029 065

Publication Number: WO 2006/020984

IPC: A61K 9/14

Language of the proceedings: EN

Title of invention:
Cyclosporin Formulations

Applicant:
TEVA PHARMACEUTICAL INDUSTRIES LTD.
(for all designated states except BB, US)
TEVA PHARMACEUTICALS, USA, INC. (for BB)

Headword:
TEVA/Cyclosporin Formulations

Relevant legal provisions:
PCT Art. 17(3)(a)
EPC Art. 154(3), 150(2)
PCT R. 13, 40.2, 40.1

Keyword:
"Reasoning of ISA insufficient"
"Reimbursement of two search fees"

Decisions cited:
W 0020/06, W 0018/06

Catchword:
There is no conflict between Rule 40.2(c) PCT as in force from 1 April 2005 and Article 154(3) EPC; Article 150(2), third sentence, EPC does not apply.

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Case Number: W 0012/06 - 3.3.02

International Application No. PCT/US 2005/029 065

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 10 September 2007

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Subject of this decision:

Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 23 February 2006.

Composition of the Board:

Chairman: H. Kellner
Members: A. Lindner
T. Bokor

Summary of Facts and Submissions

I. The applicant filed an international patent application PCT/US 2005/029065 comprising a set of 34 claims. The independent claims read as follows:

"1. A composition for reducing the variability of the bioavailability of a drug comprising cyclosporine dissolved in an effective amount of menthol and at least one surface active agent.

7. A method for reducing the variability of the bioavailability of cyclosporine comprising dissolving cyclosporine in an effective amount of menthol in the presence of at least one surface active agent.

14. A method for increasing the time that cyclosporine provides a therapeutically significant concentration in blood or plasma comprising dissolving cyclosporine in an effective amount of menthol in the presence of at least one surface active ingredient.

16. A composition for improving the bioavailability of cyclosporine comprising about 10% by weight cyclosporine dissolved in about 40% menthol, about 34% Tween 80, and about 17% ducosate sodium, wherein the weights are in percents of the composition.

19. A composition for improving the bioavailability of a drug comprising simvastatin dissolved in an effective amount of menthol.

21. A composition for improving the bioavailability of a drug comprising simvastatin dissolved in an effective

amount of menthol, wherein the composition has an average AUC_t of about 181% as compared to a non-menthol containing formulation.

24. A composition for improving the bioavailability of a drug comprising simvastatin dissolved in an effective amount of menthol, wherein the composition has an average AUC_I of about 127% as compared to the sequential administration of simvastatin and menthol.

26. A composition for improving the bioavailability of an active metabolite of a drug comprising simvastatin dissolved in an effective amount of menthol, wherein the composition has an average AUC_t for simvastatin hydroxyacid of about 143% as compared to a non-menthol containing formulation.

30. A composition for reducing the variability of the bioavailability of an active metabolite of a drug comprising simvastatin dissolved in an effective amount of menthol, where the composition has a %CV for AUC_t for simvastatin hydroxyacid which is at least about 30% lower when compared to a non-menthol containing formulation.

31. A composition for improving the bioavailability of a drug comprising raloxifene HCl and an effective amount of menthol, wherein the raloxifene HCl and the menthol are administered concomitantly.

33. A composition for improving the bioavailability of a drug comprising raloxifene HCl and an effective amount of menthol, wherein the raloxifene HCl and the menthol are administered concomitantly and the

composition has an average AUC of about 108% as compared to a non-menthol containing formulation."

II. In its communication dated 23 February 2006, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to pay two additional search fees.

III. The following documents were cited by the ISA:

(1) WO 03/082247
(2) WO 03/041632
(3) US-A-6 635 617
(4) Journal of Controlled Release, 1998, 50, pp. 297-308, P.W. Stott et al., "Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen"
(5) International Journal of Pharmaceutics, 2000, 206, pp. 35-42, L. Kang et al., "Physicochemical studies of lidocaine-menthol binary systems for enhanced membrane transport"
(6) Journal of Pharmaceutical Sciences, 1997, 86(12), pp. 1394-1399, Y. Kaplun-Frischoff and E. Touitou, "Testosterone Skin Permeation Enhancement by Menthol through Formation of Eutectic with Drug and Interaction with Skin Lipids"

IV. The ISA defined the use of menthol to increase the bioavailability of a drug in a pharmaceutical composition as the single general concept of the invention and came to the conclusion that each of documents (1) to (6) anticipated this single general

concept. As a consequence, the subject-matter as claimed did not meet the requirements of Rule 13 PCT.

The following groups of inventions were identified:

Group 1: claims 1-18

A composition for reducing the variability of the bioavailability of a drug comprising cyclosporine dissolved in menthol

Group 2: claims 19-30

A composition for improving the bioavailability of a drug comprising simvastatin dissolved in menthol

Group 3: claims 31-34

A composition for improving the bioavailability of a drug comprising raloxifene HCl dissolved in menthol

V. With his reply dated 17 March 2006, the applicant paid two additional search fees under protest pursuant to Rule 40.2(c) PCT and requested that the application be searched in its entirety and the additional search fees be refunded.

In support of the protest, the applicant argued that none of the cited prior art documents related to the ability of menthol to reduce the variability in the bioavailability of the desired drug and/or to increase the pharmacokinetic parameters of the drug. At least one of these properties of menthol constituted a common novel and inventive concept that linked all claims to a unitary invention.

VI. In the review pursuant to Rule 40.2(c) PCT dated 22 May 2006, the review panel of the ISA came to the conclusion that the invitation to pay additional fees was justified and that, as a consequence, the two additional search fees were not to be refunded. In its argumentation, the review panel defined the use of menthol as solvent to increase the bioavailability of a drug as "common special technical feature" which was, however, known in the prior art so that there was lack of unity.

VII. With the letter of 21 June 2006, the applicant paid the protest fee according to Rule 40.2(e) PCT.

Reasons for the Decision

1. Given that the international application under consideration has an international filing date of 12 August 2005, the protest is subject to the provisions of the PCT in force as from 1 April 2005, including amended Rule 40 PCT.

2. The amendments to the PCT, however, do not alter the fact that this board of appeal is competent under Article 154(3) EPC to decide on the protest made by the applicant in the present case. The decision on the board's competence in the present case is based on the same reasons as those set out in the decisions W 0020/06 of 3 April 2007 and W 0018/06 of 5 March 2007, (see for instance points 2 to 9 of the Reasons for the Decision in W 0020/06).

3. As far as the payment of fees is concerned, the applicant was invited with the communication of 22 May 2006 ("Form PCT/ISA/228 (April 2005)") to pay the protest fee within one month. In a letter dated 21 June 2006 the applicant requested the debiting of the protest fee from his Deposit Account. Thus, the payment was made in time, and the protest is considered to have been made (Rule 40.2(e) PCT, second sentence). Again, the board follows the arguments and conclusions of W 0020/06 of 3 April 2007 and W 0018/06 of 5 March 2007 (see for instance points 10 to 20 of the Reasons for the Decision in W 0020/06).

4. Moreover, the protest complies with the requirements of Rule 40.2(c) PCT and is therefore admissible.

5. The general requirements for protest proceedings are as follows:

5.1. Pursuant to Rule 40.2 PCT, the protest has to be examined and, to the extent that it is found to be justified, the full or partial reimbursement to the applicant of additional fees, as far as they were paid in fact and under protest, has to be ordered.

5.2. According to the established practice of the boards of appeal, the examination in protest proceedings has to be carried out in the light of the reasons given by the ISA in its invitation to pay additional fees under Rule 40.1 PCT and the applicant's submissions in support of the protest.

6. In the present case, the ISA's invitation to pay additional fees is based on the finding that the single

general concept of the present application is not novel over any of documents (1) to (6). It remains therefore for the board to examine whether the reasons given in accordance with Rule 40.1 PCT justify the demand for two additional fees:

6.1. The examination of unity of invention requires as a precondition an analysis of the technical problem or problems underlying the respective group of inventions. In the present case, three technical problems of the invention are directly indicated by the wording of the claims:

(a) claims 1-13 and 30 concern the reduction in the variability of the bioavailability, which in the description is defined as the relative standard deviation (CV%) of the drug's AUC (total area under the curve) over the subjects to whom the drug was administered (cf. page 7, lines 33-34);

(b) claims 14-15 relate to the increase in the time that a drug (cyclosporine) provides a therapeutically significant concentration in the blood or the plasma. According to page 7, lines 26-31 of the description, the term "therapeutically significant" is equivalent to "therapeutically effective";

(c) claims 16-29 and 31-34 are directed to the improvement of the bioavailability which according to the description on page 7, lines 8-25, refers to an increase in the blood or plasma concentration of a drug.

It follows therefrom that the subject-matter as claimed relates to three distinct technical problems which are all correlated with bioavailability, but not each of them actually increases it (see in particular problem (a)). These problems are to be solved with respect to three different drugs.

6.2. Any attempt to formulate a single general concept must take into consideration the three technical problems as defined above and it must then be examined whether the groups of inventions based on these technical problems are or are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

However, the ISA merely stated: "The general common concept of the present invention is the use of menthol to increase the bioavailability of a drug in a pharmaceutical composition." In doing so, the ISA acknowledged the existence of a single general concept, thereby excluding non-unity *a priori*; however, the single general concept was restricted to problem (c) as defined above which means that substantial parts of the invention, i.e. the subject-matter relating to problems (a) and (b) were excluded. It follows therefrom that the single general concept was not correctly defined. The ISA, apart from a very general statement that "neither the description, nor the claims revealed any further features that could be considered special in the sense of Rule 13(1) PCT", did not provide any further arguments. In the absence of a correctly defined single general concept, the applicant was not in a position to correctly interpret the reasoning of the ISA and to react accordingly.

6.3. Moreover, the grouping of the three inventions itself is not consistent: as can be seen in paragraph IV (Facts and Submissions) above, the group of inventions 1 according to the invitation to pay additional fees includes claims 1-18 and appears to concern problem (a) only. This finding is correct for claims 1-13 but wrong for claims 14-15 which concern problem (b) and 16-18 which relate to problem (c). Thus, claims 14-15 and 16-18 were included in a group of inventions to which, in terms of their actual content, they do not belong.

The same applies to the group of inventions 2 which, according to the invitation to pay additional fees, concerns problem (c) and encompasses claims 19-30. Problem (c) is indeed represented in claims 19-29, but it is not to be found in claim 30, which relates to problem (a).

As a consequence, the reasoning of the ISA is clearly insufficient.

7. In view of the insufficient and contradictory reasoning of the ISA as explained above, the invitation to pay two additional search fees is not justified and the fees paid for two additional inventions cannot be retained.

8. To conclude, as was pointed out in paragraph 5.2 above, the board only had to examine whether, considering the reasons given by the ISA and the submissions made in support of the protest, retaining additional fees was justified, and could not investigate *ex officio* whether an objection of lack of unity would have been justified

for reasons other than those given. It is therefore possible that the objection of lack of unity could be raised again on different grounds in subsequent proceedings.

Order

For these reasons it is decided that:

Reimbursement of the additional search fees paid for two inventions is ordered.

The Registrar: The Chairman:

R. Schumacher H. Kellner