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Datasheet for the decision of 27 June 2017

Case Number: T 1936/13 - 3.3.07

Application Number: 06841451.5

Publication Number: 1965773

IPC: A61K9/32, A61K31/551

Language of the proceedings: EN

Title of invention:
ORAL FORMULATION OF ANHYDROUS OLANZAPINE FORM I

Patent Proprietor:
Laboratorios Lesvi, S.L.

Opponents:
Dr Schüssler Andrea
Agrobiogen GmbH Biotechnologie

Headword:
OLANZAPINE/Lesvi

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main and auxiliary requests (no); bonus effect.

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Case Number: T 1936/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 27 June 2017

Respondent (Patent Proprietor)	Laboratorios Lesvi, S.L. Av. Barcelona 69 08970 Sant Joan Despi (ES)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Appellant: (Opponent 1)	Dr Schüssler Andrea Zeisigweg 16a 81827 München (DE)
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Appellant: (Opponent 2)	Agrobiogen GmbH Biotechnologie Thalmannsdorf 25 86567 Hilgertshausen (DE)
Representative:	Becker, Eberhard Patentanwälte Becker, Kurig, Straus Bavariastrasse 7 80336 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 August 2013 concerning maintenance of European Patent No. 1965773 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 1 965 773, based on European patent application No. 06841451.5, was granted on the basis of nineteen claims.

II. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed. Opponent 3 withdrew its opposition in the course of the first-instance proceedings.

The following documents were among those cited during the first-instance proceedings:

D1: US 2001/0018071
D2: WO2005/009407
D4: WO03/055438
D6: WO96/01874
D22: WO2006/013435
Annex 1-3: Experimental report submitted on 10 May 2013
HBP57: Pharmaceutical dosage forms and drug delivery systems, 7th Edition, 1999

III. By an interlocutory decision posted on 2 August 2013, the opposition division maintained the patent in amended form. The decision was based on the main request filed on 10 May 2013, and on auxiliary request 1 filed during the oral proceedings held on 11 July 2013.

Claim 1 of auxiliary request 1 maintained by the opposition division read as follows:

"1. Solid oral formulation of olanzapine in the form of a tablet characterised in that it comprises a tablet core of anhydrous olanzapine Form I as active substance, wherein the anhydrous olanzapine Form I has the following X-ray diffraction pattern: ...

(There follows a table containing the positions of the peaks (°2θ) and the interplanar distances (d) of the X-ray diffraction pattern)...

and, pharmaceutically acceptable excipients, wherein said tablet core has been obtained by direct compression or by dry granulation, with said tablet core being coated with a functional polymer soluble in aqueous media that acts as filmogenic agent".

IV. In its decision the opposition division came to the conclusion that the subject-matter of the main request was not novel over document D1.

The olanzapine formulations defined in auxiliary request 1 were novel over D1 on account of the requirement that they were produced by direct compression or dry granulation. As to inventive step, the opposition division held that the formulation of claim 1 of auxiliary request 1 differed from the formulations disclosed in the closest prior art D4 in that it was manufactured by a dry process and it was coated with a functional polymer soluble in aqueous media. In the light of the experimental data submitted by the patent proprietor, the technical problem was the provision of a stable formulation of anhydrous olanzapine form I with compound stability and content uniformity. Neither the use of direct compression or dry granulation nor the application of a coating as

defined in claim 1 was suggested by the available prior art. Auxiliary request 1 was therefore inventive.

V. Opponents 1 and 2 (hereinafter: appellant-opponent 1 and appellant-opponent 2) appealed the decision of the opposition division.

VI. An appeal was lodged also by the patent proprietor but it was subsequently withdrawn by letter sent on 26 May 2017.

VII. With letter of 26 June 2014 the patent proprietor (hereinafter: the respondent) requested to dismiss the appeals of the opponents and submitted four auxiliary requests.

Auxiliary request 1 and the request maintained by the opposition division differed only in claim 15. Thus, claim 1 of auxiliary request 1 was identical to claim 1 of the request maintained by the opposition division (see point III above).

Claim 1 of auxiliary request 2 was based on claim 1 of auxiliary request 1 but differed in that it indicated that the functional polymer was polyvinyl alcohol.

Claim 1 of auxiliary requests 3 and 4 corresponded to claim 1 of auxiliary requests 1 and 2 respectively, except that the tables containing the X-ray data included the relative intensities of the peaks too.

In its reply to the appeals the respondent submitted the following document:

D70: Experimental data - Lesvi Laboratorios

VIII. In a communication pursuant to Article 15(1) RPBA issued on 10 May 2017 the Board stated that it agreed with the opposition division that document D4 was a suitable starting point for the assessment of inventive step and that it related to the same olanzapine crystalline form as the patent in suit. It also observed that olanzapine was known to be moisture-sensitive. It therefore appeared that the skilled person would have avoided manufacturing methods involving humid conditions.

IX. In its letter of 26 May 2017 announcing the withdrawal of its appeal, the respondent also communicated its decision not to attend the oral proceedings scheduled for 27 June 2017.

Observations on the withdrawal of the appeal of the patent proprietor were filed by appellant-opponent 1 by letter of 19 June 2017. It observed *inter alia* that, in its opinion, the respondent was not defending the claims as maintained by the opposition division.

X. Oral proceedings were held on 27 June 2017 in the absence of the respondent.

XI. The appellants' arguments on inventive step starting from document D4 as the closest prior art can be summarised as follows:

The olanzapine tablets defined in the pending requests differed from the tablets disclosed in D4 in the features characterising the coating system and in that the core of the tablets was prepared by direct compression or dry granulation. There was no convincing evidence of any improvement arising from these distinguishing features. In any case, even it were

acknowledged that there was an improvement in stability, that did not justify the presence of an inventive activity. Indeed olanzapine was known to be metastable and moisture-sensitive. Thus, it would have been obvious to a skilled person to use dry conditions for the manufacturing process, as suggested for instance in HBP57. It would have also been obvious to coat the tablets. In particular, it was known from D6 that the use of polyvinyl alcohol-based coatings did not interfere with the tablets' disintegration time. As to the alleged improvement in content uniformity, this effect, if acknowledged, was to be regarded as a bonus effect which did not make the tablets inventive.

XII. The respondent's arguments on inventive step, can be summarised as follows:

The olanzapine crystalline form disclosed in D4 was not unambiguously the same form used in the tablets of the present invention. Furthermore, document D4 referred to several dosage forms but it did not disclose a tablet having the same features as those defined in the requests in suit. The experiments described in Annex 3 and in D70 showed the improvements achieved by the invention, namely enhanced chemical and polymorphic stability and better content uniformity. Thus, the objectives defined in the patent, in particular the provision of tablets with improved stability and of a process that preserved the crystalline form of olanzapine and ensured the tablets' uniformity had been achieved. Document D4 said nothing about the method for manufacturing the core of the tablets and the coating system. Document D6 did not address the problem of manufacturing stable olanzapine formulations. Thus, a skilled person had no reason to choose the coating systems disclosed in it. Concerning auxiliary request

2, the selection of polyvinyl alcohol as the functional polymer for the coating system resulted in an additional advantage, namely the tablets had a better dissolution profile. This effect was not suggested in any of the prior art documents.

XIII. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondent requested in writing that the appeals be dismissed (main request); alternatively, that the decision under appeal be set aside and that the patent be maintained on the basis of one of the auxiliary requests 1 to 4 filed by letter of 26 June 2014.

Reasons for the Decision

Main request (request maintained by the opposition division)

1. In its written submissions, the respondent did not make any explicit reference to the request maintained by the opposition division. In the light of this, appellant-opponent 1 commented in its letter of 19 June 2017 that the respondent was not defending the set of claims maintained by the opposition division.

However, in its reply to the opponents' appeals, the respondent stated that it "requested to dismiss the appeals filed by opponents I and II" (page 1). This is equivalent to a request for confirmation of the opposition division's decision. Hence, the set of claims maintained by the opposition division is part of the appeal proceedings.

2. Inventive step

2.1 The invention underlying the patent in suit relates to a solid oral formulation for the administration of anhydrous olanzapine form I (see [0001] of the patent).

2.2 Closest prior art

2.2.1 In agreement with the position expressed by the parties, the Board considers document D4 to be a suitable starting point for the assessment of inventive step.

2.2.2 Document D4 relates to crystalline form I of olanzapine. The respondent expressed some doubts as to whether this crystalline form was the same form described in the patent in suit. In the Board's view, the respondent's position is unjustified. D4 identifies olanzapine form I in the last paragraph of page 4 by reference to the interplanar spacing values of the X-ray diffraction pattern. These values correspond to a large extent to the d-values of claim 1 of the request under consideration. Moreover, paragraph [0022] of the patent in suit states that olanzapine form I according to the present invention is the polymorphic form I disclosed in the patent application D22. D22 (the applicant of which is the current respondent) indicates that said form I of olanzapine is disclosed in various documents including document D4 (page 2, lines 15 to 18). Thus, the polymorphic form of olanzapine described in D4 is the same polymorphic form of olanzapine in the patent in suit.

2.2.3 Document D4 discloses suitable oral dosage forms for olanzapine form I in generic terms, including coated

tablets (page 8, line 31, to page 9, line 19). However, D4 fails to disclose any specific dosage form.

Thus, the subject-matter of claim 1 differs from the disclosure of D4 on account of the features characterising the tablet's coating system and those concerning the core, which are expressed by reference to the methods of its preparation, namely direct compression or dry granulation.

2.3 Technical problem

2.3.1 On the basis of the experimental results disclosed in Annex 3 and D70, the respondent maintained that the tablets of claim 1 had advantageous properties in terms of chemical and polymorphic stability. It also argued that the manufacturing process resulted in an improvement in content uniformity.

These conclusions were disputed by the appellants.

2.3.2 As, even if improvements in stability and content uniformity are acknowledged - as would be in the respondent's favour - the conclusion is reached that there is no inventive step (see point 2.4 below), the Board does not need to decide on this point.

The Board will therefore examine inventive step based on the assumption that the technical problem is the provision of a coated tablet of anhydrous olanzapine form I with improved stability and content uniformity.

2.4 Obviousness

2.4.1 Olanzapine (regardless of its polymorphic form) was known at the priority date of the patent in suit to be

moisture-sensitive (see D1 paragraph [0006] and D2 paragraph [3]). This fact would have immediately prompted the skilled person faced with the problem of providing olanzapine tablets and concerned with issues of stability to avoid manufacturing processes involving humidity and to opt instead for a dry method. As stated by the respondent (page 14 of the reply to the appeals) and by appellant-opponent 1 (page 16 of the letter of 31 January 2017), there are only three conventional methods for preparing tablets, i.e. wet granulation, direct compression and dry granulation. The exclusion of wet granulation would have directed the skilled person to select one of the two remaining methods, which are both recited in claim 1. Furthermore, an explicit suggestion along these lines is provided by document HBP57, which recommends using dry granulation for materials that cannot be processed by wet granulation due to their degradation by moisture (page 213, left column, first complete paragraph). Thus, the selection of direct compression or dry granulation was obvious to the skilled person seeking to provide an olanzapine tablet of enhanced stability.

2.4.2 Protecting a solid oral formulation containing olanzapine with a coating system in order to prevent degradation of the active ingredient is suggested by D1 (paragraph [0007]). The use of a coating system as a barrier against moisture is also suggested in document D6 (page 3, lines 13 to 21). Although D6 makes no mention of olanzapine, the skilled person would have considered the teaching of this document since it provides a solution to the problem of formulating moisture-sensitive compounds in stable pharmaceutical tablets (page 1, lines 5 to 17). The coating system described in D6 is a water-soluble composition based on polyvinyl alcohol (page 3, line 13 to page 4, line 13).

Example 1 describes in particular a coating system containing polyvinyl alcohol, talc, titanium dioxide and soya lecithin. The same ingredients are included in the coating described in paragraph [0061] of the patent in suit. D6 indicates that the water-soluble coatings that it describes have excellent moisture-barrier properties (page 5, lines 12 to 20) and that compared with coating systems based on water-insoluble polymers, the coatings of D6 have a negligible effect on the tablet's disintegration time (page 18, lines 16 to 20).

Thus, it would have been evident to a skilled person to use a coating system based on a polymer soluble in aqueous media in order to preserve the stability of olanzapine tablets.

2.4.3 As to the improvement in content uniformity, the Board agrees with the appellants that this is a bonus effect which does not make the tablets of claim 1 inventive.

In the respondent's opinion, manufacturing the olanzapine tablets by direct compression or dry granulation improved the content uniformity. However, as explained in point 2.4.1 above, the skilled person seeking to provide highly stable olanzapine tablets would have avoided using wet granulation for their preparation anyway since the active ingredient is moisture-sensitive. This would have forced him to select a dry method, namely direct compression or dry granulation. In other words, when addressing the first part of the technical problem (improving the tablets' stability) the skilled person would have had no alternative to choosing one of the two methods recited in claim 1. In such a "one-way-street" situation, the existence of an additional effect, not taught by the prior art documents, does not render the subject-matter

of the claim inventive (Case Law of the Boards of Appeal of the EPO, 8th Edition 2016, I.D.10.8).

2.5 The Board therefore concludes that claim 1 of the main request does not meet the requirements of Article 56 EPC.

Auxiliary request 1

3. Claim 1 of this request is identical to claim 1 of the main request. Thus, auxiliary request 1 is not inventive either.

Auxiliary request 2

4. Claim 1 of auxiliary request 2 differs from claim 1 of the main request in specifying that the polymer used for the coating of the tablet is polyvinyl alcohol.

4.1 On the basis of the experimental results disclosed in D70, the respondent argued that a polyvinyl alcohol-based coating system did not modify the dissolution rate of the tablets. By contrast, the use of polymers soluble in organic media for the coating system resulted in a significant delay in the release of the active ingredient.

4.2 As discussed in point 2.4.2 above, document D6 discloses the same polyvinyl coatings described in the patent in suit. Furthermore, this document points out that these coatings do not affect the tablet's disintegration time and therefore do not interfere with the release of the active ingredient (page 18, lines 16 to 20).

4.3 In view of the above, claim 1 of auxiliary request 2 is also not inventive.

Auxiliary requests 3 and 4

5. Claim 1 of auxiliary requests 3 and 4 is based on claim 1 of the main request and of auxiliary request 2 respectively, with the difference that the tables defining the X-ray diffraction pattern includes also the peaks' relative intensities too.

This amendment was introduced in relation to an objection under Article 123(2) EPC and has no influence on the assessment of inventive step. Indeed the respondent did not submit any specific arguments on the inventive step of these requests. Therefore, auxiliary requests 3 and 4 do not comply with the requirements of Article 56 EPC for the same reasons as for claim 1 of the main request and of auxiliary request 2.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated