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Datasheet for the decision of 16 October 2012

Case Number: T 1572/08 - 3.3.02

Application Number: 04737220.6

Publication Number: 1499278

IPC: A61K 9/20, A61K 31/567

Language of the proceedings: EN

Title of invention:
Immediate-release pharmaceutical dosage form comprising polymorphous tibolone

Patentee:
MSD Oss B.V.

Opponents:
Tecnimede Sociedade Técnico-Medicinal, S.A.
Tiefenbacher Pharmachemikalien Alfred E. Tiefenbacher (GmbH&Co.KG)
LABORATORIOS LEÓN FARMA S.A.
NORTON HEALTHCARE LTD
Neolab Limited

Headword:
-

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty, main request (yes)"
"Inventive step, main request (no): problem not plausibly solved"

Decisions cited:
-

Catchword:
-

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Case Number: T 1572/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 16 October 2012

Appellant: (Patent Proprietor)
MSD Oss B.V.
Kloosterstraat 6
NL-5349 AB Oss (NL)

Representative:
Hussain, Deeba
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU (GB)

Respondent I: (Opponent 1)
Tecnimede Sociedade Técnico-Medicinal, S.A.
Rua Professor Henrique de Barros
Edificio Sagres, 3 A
PT-2685-338 Prior Velho (PT)

Representative:
HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastraße 4
D-81925 München (DE)

Respondent II: (Opponent 2)
Tiefenbacher Pharmachemikalien Alfred E.
Tiefenbacher (GmbH&Co.KG)
Van-der-Smissen-Strasse 1
D-22767 Hamburg (DE)

Representative:
Hamm, Volker
Maiwald Patentanwalts GmbH
Jungfernstieg 38
D-20354 Hamburg (DE)

Respondent III: (Opponent 3)
LABORATORIOS LEÓN FARMA S.A.
Roa de la Vega 15
ES-24002 Leon (ES)

Representative:
Markvardsen, Peter
ZBM Patents
Zea, Barlocci & Markvardsen
C4 Videncenter
Krakasvej 17
DK-3400 Hilleroed (DK)

Respondent IV: (Opponent 4)	NORTON HEALTHCARE LTD Albert Basin Royal Docks London E16 2QJ (GB)
Representative:	ter Meer, Nicolaus ter Meer Steinmeister & Partner GbR Mauerkircherstrasse 45 D-81679 München (DE)
Respondent V: (Opponent 5)	Neolab Limited 57 High Street, Odiham Hook, Hants RG29 ILF (GB)
Representative:	Grünecker, Kinkeldey Stockmair & Schwanhäusser Leopoldstrasse 4 D-80802 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 13 June 2008 revoking European patent No. 1499278 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: A. Lindner
Members: D. Boulois
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 499 278, which was filed as application number 04737220.6, based on international application WO 2004/103378, was granted on the basis of 7 claims.

Claim 1 as granted read as follows:
"1. An immediate-release pharmaceutical dosage form comprising, as the active substance, polymorphous tibolone and pharmaceutically acceptable excipients, wherein the polymorphous tibolone has a mean particle size of below 22.8 µm in the dosage form."

II. Oppositions were filed and revocation of the patent in its entirety was requested pursuant to Article 100(b) for lack of disclosure and 100(a) EPC for lack of novelty and inventive step.

III. The documents cited during the opposition and appeal proceedings included the following:
(3) WO 03/032924
(7) U.V. Banakar, "Pharmaceutical Dissolution Testing", 1992, Marcel Dekker, Inc., pages 136-137 and 144-145
(8) L. Lachman et al., "The Theory and Practice of Industrial Pharmacy", Third Edition, Lea & Febiger, 1986, Philadelphia, pages 221-222
(10) "Pharmaceutical Dosage Forms, Tablets", Second Edition, Edited by H.A. Lieberman, L. Lachman, J.B. Schwartz, Marcel Dekker, Inc., New York and Basel, 1990, pages 107-112
(21) Declaration of Dr. Alberto SALA, Industriale Chimica SRL, Italy

(27) "Pharmazeutische Technologie", 5. Auflage, K.H. Bauer, K.H. Frömming, C. Führer, Stuttgart Jena Lübeck Ulm, Govi-Verlag Frankfurt, 1997, pages 209-210 and 365
(29) Basic principles of particle size analysis, Dr Alan Rawle
(30) Lagace M. et al, Dissolution Technologies, February 2004, pages 13-17
(38a) Certificate of Analysis
(38b) Coulter® LS Particle Size Analyzer
(38c) Helos Particle Size Analysis

IV. The present appeal lies from a decision of the opposition division pronounced on 22 April 2008, revoking the patent (Article 101(1) and (3)(b) EPC 1973) for lack of inventive step of the main request filed during the oral proceedings.

In said decision, the opposition division considered that the requirements of Article 83 EPC were met, because a skilled person would be able to produce an immediate release dosage form containing polymorphous tibolone.
As regards the claimed particle size, it was apparent to a skilled person that the size of the tibolone inside a dosage form could not be measured directly. However, the opposed patent provided an indirect method of measurement of the particle size based on a dissolution test of the dosage form (par. [0055]-[0077]), since the correlation between dissolution rate and particle size was generally valid in the case of immediate release dosage forms (par. [0019]).
It was furthermore apparent to the skilled person that a tibolone particle size of below 22.8 µm could easily

be achieved by controlling the initial particle size of the tibolone.

As regards novelty, the opposition division considered that none of the documents, in particular document (3), contained a direct and unambiguous disclosure of a tibolone mean particle size of below 22.8 µm in the dosage form.
The statement of document (21) could not provide full evidence that the tibolone used in document (3) and the sold batches were unambiguously one and the same product.

As regards inventive step, the problem to be solved by the patent was the provision of an immediate release dosage form of tibolone, as an alternative to the marketed product Livial®, and offering a bioavailability of 3α-OH-tibolone of at least the same level as that of a solution of tibolone.
The closest prior art was document (3), and the objective problem to be solved was the provision of an alternative dosage form for tibolone, comprising polymorphous tibolone. The only difference between the subject-matter claimed in the opposed patent and the disclosure of document (3) was that the latter did not specify any particular range of particle size of tibolone in the dosage form.
It was however customary in the field of drug formulation to micronise poorly soluble drugs in order to enhance their dissolution and absorption in aqueous media, as shown by documents (7), (8), (10) and (27).
The skilled person would regard it as an obvious and straightforward measure to control the particle size and bioavailability, especially when considering the

known and expected dissolution problems of polymorphous tibolone referred to in document (3). Such a selection did not involve an inventive step and the increase in bioavailability shown was not unexpected.
Thus, the subject-matter claimed in the main request submitted during the oral proceedings on 22 April 2008 before the opposition division lacked inventive step over document (3).

V. The patent proprietor (appellant) filed an appeal against said decision.
Documents (35),(36) and (37) were filed with the statement of grounds of appeal.

Claim 1 of the main request, which corresponds to the main request submitted during the oral proceedings before the opposition division, reads as follows:

"1. An immediate-release pharmaceutical dosage form comprising, as the active substance, polymorphous tibolone and pharmaceutically acceptable excipients, wherein the polymorphous tibolone has a mean particle size of below 22.8 µm in the dosage form, and wherein the polymorphous tibolone contains at least two different crystal structures each present in an amount of at least 10% by weight".

VI. The respondent-opponents 01, 03 and 04 filed counter-arguments to the patentee's appeal.
Documents (38a), (38b) and (38c) were filed by respondent 04 with the letter dated 26 June 2009.

VII. Observations by a third party under Article 115 EPC were filed with a letter dated 14 December 2011.

VIII. Respondent-opponent O2 announced with a letter dated 4 October 2012 that it would not be attending the oral proceedings before the board of appeal.

IX. Oral proceedings took place on 16 October 2012.

X. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows:

As regards inventive step, the appellant agreed with the opposition division that document (3) should be the closest prior art.
The problem to be solved should be "to provide an immediate release pharmaceutical dosage form comprising polymorphous tibolone, and providing an improved bioavailability, of 3α-OH-tibolone, as compared to a solution of tibolone" (see par. [001] and [0012]).
The solution resided in providing tibolone in a pharmaceutical dosage form having a mean particle size of below 22.8 µm in the dosage form.
Document (3) proposed an additive, namely a pH adjusting agent, to improve the solubility and bioavailability of polymorphous tibolone (see document (3), par.[0007], [0013], [0044], [0045] and [0049]).
The prior art did not suggest that the bioavailability might be improved by an immediate release solid dosage form.
According to the appellant, the opposition division had dismissed the surprising improvement of bioavailability over a tibolone solution, while a comparison with the compositions disclosed in document (3) was impossible, because the particle size of the tibolone raw material used in the examples of document (3) was not known.

Document (3) did not address the problem of bioavailability, let alone offer a suggestion as to how to solve this problem.

XI. The respondents' arguments, as far as relevant for the present decision, may be summarised as follows.

According to respondent 01, document (3) was relevant for novelty, although the particle size was not explicitly disclosed in this document.
It was not possible to measure directly the size of the particles in the final dosage form, but the contested patent mentioned a dissolution test which served to determine the particle size, as a function of the specific dissolution speed.
A very similar test was present in document (3), with a different quantity of solvent and paddle rotation speed. This test gave a dissolution time of 88 to 100% in 15 minutes. By calculation, this time corresponded to a T_{50} of 22 minutes, which was less than the 23.1 minutes presented in the patent in suit as the time of dissolution corresponding to a particle size as claimed. There was indeed a direct relationship between the volume and the rotation speed between the tests.
Document (30) allowed a prima facie assumption that the calculation was correct (see document (30) page 16, figure 5).

Moreover, document (21) proved that the tibolone used in the formulation A of document (3) had a particle size within the limits of the patent in suit. The claimed particle size was inherent to all tibolones obtained by Industriale Chimica SRL, which was the product used in the examples of the contested patent.

As regards inventive step, respondent 01 considered that document (3) had to be regarded as the closest prior art. Assuming that formulation A of document (3) was not novelty-destroying for the claimed subject-matter, the feature distinguishing the claimed subject-matter from the closest prior art was the particle size of below 22.8 µm.
According to the patentee, reducing the particle size led to better bioavailability, which was already known from the literature, as shown by documents (7), (8) and (27).
Furthermore, the "mean particle size" that formed a distinguishing feature over the closest prior art was not an adequate measure to characterise the particle size of a sample. Whether the particles had an overall size that was numerically similar to the average value, or whether the sample was composed of an amount of large-sized particles and an amount of small-sized particles, the mean particle size would be the same, but in the latter case the problem underlying the patent would not be solved over the whole scope of the claims.

The arguments of respondents 03 and 04 were essentially the same than those from respondent 01 as regards novelty and inventive step.

As regard novelty, respondent 04 considered additionally that there was full evidence that the tibolone used in document (3) and the sold batches referred to in document (21) were one and the same product and fulfilled the requirements of claim 1 of the contested patent. Documents (38a), (38b) and (38c)

showed that the batch of tibolone number 02011, a typical batch produced by Industriale Chimica SRL in February 2002 and also used in example 2 of document (3), had the claimed characteristics. Document (38a) showed that for the said batch 020111, the content of polymorph 2 was 13%, while document (38b) showed that the mean particle size according to the Coulter data was 13.61 µm, and document (38c) gave for the same batch a mean diameter $d_{(4,3)}$ of 12.37 µm.

XII. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request submitted on 22 April 2008.

The respondents (opponents 01, 03, 04) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request - Novelty*

2.1 The subject-matter of Claim 1 of the main request relates to an immediate-release pharmaceutical dosage form comprising a polymorphous tibolone with a mean particle size of below 22.8 µm, and at least two different crystal structures present in an amount of at least 10% by weight.

2.2 Document (3) discloses a tablet comprising tibolone at a polymorphic ratio of 85% of form I and 15% of form II,

obtained by compression with excipients chosen among lactose, pre-gelatinised starch, ascorbyl palmitate, sodium citrate, sodium lauryl sulphate, croscarmellose sodium and magnesium stearate (see document (3), Formulation A in Table IV, page 11, and examples 2 and 3).
The nature of the excipients, and the final structure of the tablet, in particular the absence of any external coating, qualifies this compressed tablet as an immediate-release dosage form.
Document (3) is however completely silent on the particle size of the polymorphous tibolone used in examples 2 and 3.

According to the description of the patent in suit, a correlation between the particle size and the speed of dissolution of the immediate release dosage form in a standardised dissolution test is generally valid (see specification, par. [0019], [0057], [0072]). A t_{50} value, i.e. the time at which 50% of the tibolone is dissolved, of below 23.1 minutes, obtained in 500 ml of a specific dissolution medium at a paddle speed of 50 r.p.m., correlates with a mean particle size of below 22.8 µm.
A very similar dissolution test is performed in document (3) on the immediate release dosage forms, with a higher paddle speed (75 r.p.m.) and a greater amount of the same dissolution medium (900 ml). In this test, a dissolution of 88% is obtained after 15 minutes.
It does not however seem possible to make an extrapolation of the results from one test to another test with modified test parameters in the form of a cross-multiplying equation. It has not been shown by

any experimental result that a simple mathematic correlation exists between the test performed in the patent in suit and the test performed in document (3). Document (30) shows for instance that the dissolution rate at different paddle speeds is not linear and not proportional.
It is all the more difficult to make an extrapolation, given the fact that the dosage forms, in particular the nature and quantities of the excipients, as well as the process of preparation, affect the dissolution speed.
In other words, it is not credible that the test presented in the patent in suit offers a precise and exact correlation between the particle size of tibolone and the dissolution speed of a dosage form comprising tibolone.
Thus, the dissolution experimentation performed in document (3) does not make it possible to determine that the mean particle size of tibolone is below 22.8 µm in the dosage form.

Consequently, it is not possible to conclude that the dosage forms disclosed in document (3) comprise tibolone presenting the claimed mean particle size.

2.3 Further evidence was provided by the respondents to support the relevance of document (3) for the question of novelty.

According to the respondents, the relevance of document (3) in connection with the particle size is demonstrated by document (21) which is a declaration by Dr. Alberto Sala of Industriale Chimica SRL.
The polymorphous tibolone used in example 2 of document (3) was indeed obtained from this company.

Document (21) was therefore provided to support the argument that all the tibolone production batches manufactured by Industriale Chimica SRL and sold to the applicants of document (3), i.e. Ivax Corporation and Norton Healthcare LTD, during the period from 1999 to May 2003 comprised polymorphous tibolone with a mean particle size of below 22.8 µm.
Dr. Sala is a chemist and "*responsible for technical issues with respect to the industrial production of the commercial available tibolone product*". However, there is no information on file as to the exact responsibilities of Dr. Sala in that company in particular, there is no evidence that he was in a position to oversee the whole production, quality control and sale of the commercial tibolone product.

Respondent 04 submitted documents (38a), (38b) and (38c) as a further evidence on the mean size and polymorphous composition of the commercial batches of tibolone sold by Industriale Chimica SRL. These documents do indeed show a batch having the claimed polymorphous structure and mean particle size. There is however no evidence that this batch was sold to the applicants of document (3), or that all batches of tibolone produced had the same physico-chemical characteristics.

2.4 Consequently, the main request is novel over document (3), and meets the requirements of Article 54 EPC.

3. *Main request - Inventive step*

3.1 The present invention relates to an immediate-release pharmaceutical dosage form comprising a polymorphous tibolone.

3.2 Document (3) constitutes the closest prior art, since it discloses an immediate-release tablet comprising tibolone at a polymorphic ratio of 85% of form I and 15% of form II. The particle size of tibolone in the final dosage form is unknown from document (3).
The choice of document (3) as closest prior art was not contested by any party.

3.3 The problem of the present invention can be defined as the provision of a dosage form of tibolone presenting an improved bioavailability (see paragraphs [0010], [0012] of the contested patent).

3.4 The solution proposed by the subject-matter of claim 1 of the main request concerns the selection of an immediate-release pharmaceutical dosage form comprising a polymorphous tibolone with a mean particle size of below 22.8 µm, and at least two different crystal structures present in an amount of at least 10% by weight.

3.5 The question is whether the problem has or not been plausibly solved.

The contested patent comprises one example of an immediate release formulation comprising tibolone having a volume mean diameter d(4,3) of 19.3 µm. Examples 2 and 3 relate to a comparison of the

bioavailability of the tablet of example 1 compared to a marketed product comprising tibolone in a pure crystalline form, a product with a higher mean particle size and a solution of tibolone. It is shown that the compositions according to example 1 have an improved bioavailability over solutions of tibolone and over dosage forms with a higher mean particle size, and a bioavailability comparable to the marketed product.

The subject-matter of claim 1 relates however to immediate release dosage forms comprising tibolone having a mean particle size without any reference in the claims to the type of measurement used to calculate the said "mean particle size", which leads to uncertainty as to the actual maximal mean size of the particles in independent claim 1. Thus, the subject-matter of claim 1 encompasses dosage forms comprising tibolone with a particle size beyond a volume mean diameter d(4,3) of 22.8 µm.

Moreover, the absence of any further technical characterisation in the claims regarding the size range and the distribution mode of the particle size of the active agent gives only an incomplete definition of the particulate structure which, as was correctly pointed out by the respondents, includes a bi-modal particle size distribution with a majority of particles with a large size and a minority of particles with a small size, the mean particle size being a value between the two. This particular polydisperse size distribution would have an obvious detrimental influence on the dissolution rate in comparison to a monodisperse particle size having a mean particle size below 22.8 µm.

As a consequence, none of the examples in the contested patent is suitable for demonstrating a beneficial effect of the entirety of the claimed subject-matter over the prior art. It is therefore not credible that the problem be solved over the whole scope of the claims.

Thus, the problem underlying the present invention can be seen only as the provision of a further immediate release dosage form of tibolone.
In view of the information found in the description of the contested patent, the board is convinced that the problem has been plausibly solved.

3.6 Thus, the question to be answered is whether the proposed solution(s) would have been obvious to the skilled person in the light of the prior art.

Documents (7), (8), (10) and (27) represent general knowledge in the field of pharmaceutical technology. They show that the reduction of the particle size of active agents is common practice for the skilled person. They also show that particle size reduction is linked to an improved rate of dissolution and bioavailability:
- document (7) discloses that reducing the size of drugs contained in tablets or capsules will enhance dissolution and absorption (see page 144, "Particle size").
- document (27) shows the influence of the reduction of particle size on the improvement of solubility (see page 209, "Einfluss der Partikelgrösse").

- according to document (8), the surface area, thus the particle size, is a parameter that influences drug dissolution and in turn drug absorption (see page 221, "Particle Size"). Small particles with greater surface area will dissolve quicker, which has a significant effect on the absorption of drugs with low aqueous solubility.
- document (10) discloses that particle size reduction enhances the dissolution rate and hence bioavailability (see page 110, Chapter 3).

The reduction of the mean particle size is therefore a common and obvious solution which can be put into practice as a matter of routine by a skilled person.

3.7 Further arguments of the appellant

According to the appellant, the objective definition of the problem solved by the invention should start from the problem defined in the patent, i.e. "*to provide an immediate release pharmaceutical dosage form comprising polymorphous tibolone, and providing an improved bioavilability of 3α-OH-tibolone, as compared to a solution of tibolone*". The prior art does not suggest that this stated goal could ever be accomplished by an immediate release dosage form. The surprising data of improved bioavailability of 3α-OH-tibolone versus a tibolone solution cannot be dismissed.
Moreover, it is not possible to make a comparison with document (3), since this document does not give any information on the particle size. It is therefore inappropriate to require a demonstration of superiority over document (3), when it is not possible to replicate any of the examples of document (3).

The board could however not follow this reasoning. It is not contested that the formulation of example 1 provides improved bioavailability over a tibolone solution and over a dosage form with a particle size beyond 22.8 µm. The solution proposed by the subject-mater of claim 1 does not however reflect the specific embodiment of example 1.
Consequently, the board does not see in the said comparative examples any evidence that the problem has been solved by the claimed subject-matter. The problem has thus to be redefined in view of the teaching of the closest prior art, which is document (3).

3.8 Thus, the subject-matter of claim 1 of the main request is obvious vis-à-vis document (3). Consequently, the main request does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. Lindner