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**Datasheet for the decision
of 24 May 2011**

Case Number: T 0777/08 - 3.3.01

Application Number: 01116338.3

Publication Number: 1148049

IPC: C07D 207/34

Language of the proceedings: EN

Title of invention:

Crystalline R-(R*, R*) β -2-(4-fluorophenyl)-beta, delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carbonyl - 1H-pyrrole-1-heptanoic acid hemi calcium salt (atorvastatin)

Patentee:

Warner-Lambert Company LLC

Opponent:

Teva Pharmaceutical Industries Ltd.

Headword:

Atorvastatin polymorphs/WARNER-LAMBERT

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

-

Keyword:

"Inventive step (no) - foreseeable improvement of crystalline vs. amorphous forms"

Decisions cited:

T 1066/03, T 1110/03

Headnote:

1. At the priority date of the patent in suit, the skilled person in the field of pharmaceutical drug development would have been aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry, and have known it to be advisable to screen for polymorphs early on in the drug development process. Moreover, he would be familiar with routine methods of screening. Consequently, in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step.

2. When starting from the amorphous form of a pharmaceutically active compound as closest prior art, the skilled person would have a clear expectation that a crystalline form thereof would provide a solution to the problem of providing a product having improved filterability and drying characteristics. The arbitrary selection of a specific polymorph from a group of equally suitable candidates cannot be viewed as involving an inventive step.

3. The skilled person in the field of drug development would not be dissuaded from attempting to obtain a crystalline form by the prospect of a potential loss of solubility and bioavailability when compared to the amorphous form, but would rather regard this as being a matter of trade-off between the expected advantages and disadvantages of these two classes of solid-state forms.



Case Number: T 0777/08 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 24 May 2011

Appellant: Warner-Lambert Company LLC
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 4 February 2008
revoking European patent No. 1148049 pursuant
to Article 101(2), (3)(b) EPC.

Composition of the Board:

Chairman: P. Ranguis
Members: L. Seymour
D. S. Rogers

Summary of Facts and Submissions

I. The patent in suit (European patent No. 1 148 049) was filed under patent application number 01 116 338.3, as a divisional application of the parent application EP-A-0 848 705, based on international application WO 97/03959. It was granted on the basis of fourteen claims relating to forms II and IV of crystalline atorvastatin hydrate, and corresponding pharmaceutical compositions and uses.

Independent claim 7 as granted read as follows (full chemical name of atorvastatin omitted by the board):

"7. Crystalline Form IV atorvastatin (...) hydrate having an X-ray powder diffraction pattern containing the following 2θ values measured using $\text{CuK}\alpha$ radiation: 7.997 and 9.680."

II. An opposition was filed and revocation of the patent in its entirety requested pursuant to Articles 100(c), 100(b) and 100(a) EPC (lack of novelty and inventive step).

III. The following documents were cited *inter alia* during the opposition/appeal proceedings:

(1) WO 94/16693

(2) EP-A-0 409 281

(10) S Byrn et al., *Pharmaceutical Research*, July 1995, 12(7), 945 - 954

- (25) Report filed at oral proceedings before opposition division, GMS-CFEP-2007-20, "Filtration and Drying Study on Amorphous and Form IV Atorvastatin Calcium"
- (27) B C Hancock et al., Pharmaceutical Research, June 1995, 12(6), 799 - 806
- (28) M Bavin, Chemistry & Industry, 21 August 1989, 527 - 529
- (30) Report EC20082069.02.01 dated 23 February 2009, filed with appellant's letter of 26 April 2011

IV. The appeal lies from the decision of the opposition division revoking the patent under Article 101(2), (3) (b) EPC.

The decision was based on a main request (the claims as granted), a first auxiliary request filed with letter of 21 September 2007, and a second auxiliary request filed during the oral proceedings before the opposition division.

The main request was found not to comply with the requirements of Article 100(c) EPC.

Concerning the first and second auxiliary requests, the opposition division was of the opinion that the requirements of Articles 100(c), 123(2), (3) and 100(b) EPC were satisfied.

Novelty was also acknowledged since no evidence had been provided that the products obtained in example A of document (1) and example 10 of document (2) exhibited the same X-ray powder diffraction patterns or solid state ¹³C NMR spectra as the crystalline forms claimed.

With respect to the issue of inventive step, the opposition division identified documents (1) and (2) as representing the closest prior art, and defined the problem to be solved as lying in the provision of further crystalline forms of atorvastatin having surprising effects compared to that disclosed in the prior art. The opposition division did not consider the comparative data provided to be pertinent since the solid-state form chosen for comparison was the amorphous form rather than the crystalline form as disclosed in documents (1) and (2). Moreover, the opposition division argued that, even were the amorphous form to be accepted as a valid point of comparison, an inventive step could not be based on the comparative data provided, since the skilled person would expect improvements in stability, filtration and drying with crystalline forms as compared to amorphous forms.

V. The appellant (patentee) lodged an appeal against this decision. Its main request was identical to the first auxiliary request considered in the decision under appeal.

VI. In its response of 6 November 2008, the respondent (opponent) did not refer to the issue of novelty, but maintained its objection of lack of inventive step,

with reference to the reasoning of the opposition division in the decision under appeal (cf. point IV above). In its letter of 23 December 2008, the respondent referred to decision T 1066/03, issued by this board in a different composition, as being relevant to the ground of opposition under Article 100(b) EPC.

VII. In a communication sent as annex to the summons to oral proceedings, the board expressed its preliminary opinion on a number of issues, and cited two further documents (27) and (28), as listed under point III above, as being relevant to the assessment of common general knowledge at the priority date of the patent in suit.

VIII. With letter of 26 April 2011, the appellant filed a new main request containing claims relating to both forms II and IV of crystalline atorvastatin hydrate, and an auxiliary request relating only to form IV. Claim 3 of the main request is identical to claim 1 of the auxiliary request, and reads as follows:

3. Crystalline Form IV atorvastatin (i.e. [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 θ , d-spacings, and relative intensities with a relative intensity of >15% measured using CuK α radiation:

2 θ	d	Relative Intensity (>15%)
4.889	18.605	38.45
5.424	16.2804	20.12
5.940	14.8660	17.29
7.997	11.0465	100.00
9.680	9.1295	67.31
10.416	8.4859	20.00
12.355	7.1584	19.15
17.662	5.0175	18.57
18.367	4.8265	23.50
19.200	4.6189	18.14
19.569	4.5327	54.79
21.723	4.0879	17.99
23.021	3.8602	28.89
23.651	3.7587	33.39
24.143	3.6832	17.23

IX. Oral proceedings were held before the board on 24 May 2011.

X. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant considered that the known amorphous form of atorvastatin as obtained in documents (1) and (2) represented the closest prior art. The problem to be solved lay in the provision of an alternative form of atorvastatin having improved characteristics with respect to filterability and drying. This problem had been solved by means of the specific polymorphs now

claimed, as demonstrated by the results of the filtration experiments presented in document (25). Although denying that it represented a prior art document in the sense of Article 54(2) EPC, the appellant referred to document (10) in order to support its position that it was part of the general knowledge of the person skilled in the art that amorphous forms were generally more soluble and bioavailable than their crystalline counterparts. Therefore, the skilled person would have no incentive to look to the latter as a solution to the above-mentioned problem. Based on the cited prior art, the skilled person could not have predicted that the specific polymorphs claimed would show the improved properties demonstrated, which made them more amenable to large-scale processing.

XI. The respondent confirmed at oral proceedings that it had no formal objections to the newly filed requests, in particular as regards Article 100(c) EPC. With respect to the issue of sufficiency of disclosure, the respondent referred to previous submissions on file. The objections with regard to novelty were not maintained. On the issue of inventive step, the respondent again referred to the reasoning of the opposition division in the decision under appeal.

XII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or alternatively on the basis of the auxiliary request, both filed under cover of the letter dated 26 April 2011.

The respondent (opponent) requested that the appeal be dismissed.

XIII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments (Articles 100(c), 123(2), (3) EPC)*

The board is satisfied that the amended claims according to the main request and auxiliary request are formally allowable. This was not contested by the respondent.

3. *Sufficiency of disclosure (Articles 100(b), 83 EPC)*

In view of the outcome of these appeal proceedings on the question of inventive step (see point 5 below), it is not necessary to discuss sufficiency of disclosure.

4. *Novelty (Articles 52(1), 54 EPC)*

In the experimental report filed as document (30), the appellant has demonstrated that repetition of the "recrystallisation" step under the conditions used in example A of document (1) and example 10 of document (2) yields an amorphous solid. Accordingly, the board is satisfied that the claimed polymorphs of atorvastatin hydrate as claimed in the main and auxiliary requests

are novel over the cited prior art. The respondent did not contest this finding.

5. *Inventive step (Articles 52(1), 56 EPC)*

5.1 As outlined above under point VIII, claim 3 of the main request and claim 1 of the auxiliary request are identical and relate to form IV of crystalline atorvastatin hydrate.

The board considers, in agreement with the appellant, that the amorphous form of atorvastatin, as obtained according to the processes of documents (1) and (2) (see point 4 above), represents the closest state of the art.

The appellant defined the problem to be solved in view of this prior art as lying in the provision of atorvastatin in a form having improved filterability and drying characteristics.

The solution as defined in claim 3 of the main request and claim 1 of the auxiliary request relates to a specific polymorph of atorvastatin.

Having regard to the experimental results reported in document (25), which demonstrate shorter filtration and drying times for form IV compared to the amorphous form, the board is satisfied that this problem has been solved.

5.2 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art and the relevant common general knowledge.

The skilled person in the field of pharmaceutical drug development would have been aware of the common general knowledge as reflected by documents (10), (27) and (28).

It is noted in this context that the appellant has disputed that document (10) forms part of the state of the art within the meaning of Article 54(2) EPC. This document was printed in the July 1995 issue of the journal "Pharmaceutical Research", that is, in the same month as the present priority date of 17 July 1995. Although the exact day on which it was made available to the public could not be established, it is noted that document (10) is a review article, which is, by definition, an account of the common general knowledge and the state of the art prior to its own publication date. As will be explained in more detail below, this is corroborated by the disclosures of documents (27) and (28). Hence, the board considers document (10) to provide a legitimate basis for evidence of the common general knowledge of the skilled person at the priority date of the patent in suit (cf. T 1110/03, OJ EPO 2005, 302, reasons point 2).

From his common general knowledge, the skilled person would firstly be aware of the fact that instances of polymorphism are commonplace in molecules of interest for the pharmaceutical industry, as can, for instance, be inferred from the following passage of document (28) (see page 527, left-hand column, third paragraph):

"Polymorphs have crystal lattices which differ in the ways in which the same molecule is bound in the unit cell. The differences may reflect different ways of packing molecules in the cell, or conformational changes, which can be large. Hydrogen-bonding will be involved for most molecules of interest to the pharmaceutical industry."

The skilled person would also have known it to be advisable to screen for polymorphs early on in the drug development process, as explained in document (28), page 528, left-hand column, first paragraph (cf. also document (10), page 946, first complete paragraph):

"In giving each development candidate the best chance of progressing, it seems better to search for polymorphs rather than to leave their appearance to time and chance with the consequent disruption."

Indeed, the skilled person would also have been aware of regulatory requirements to provide information on the occurrence of polymorphic, hydrated, or amorphous forms of a drug substance (cf. document (10), page 945, left-hand column, first two paragraphs). Moreover, he would be familiar with routine methods for screening for polymorphs by crystallisation from a range of different solvents under different conditions (cf. document (28), page 528, left-hand column, first paragraph; document (10), page 946, right-hand column, last paragraph).

It follows from the above that, at the priority date of the patent in suit, it belonged to the routine tasks of the skilled person involved in the field of drug development to screen for solid-state forms of a drug substance. For the sake of completeness, the board therefore wishes to note that, in the absence of any technical prejudice, which has not been alleged by the appellant, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step (contrary to the statement in the patent in suit, paragraph [0011]). However, in the present appeal proceedings, as outlined above under point 5.1, the appellant relied in support of the presence of an inventive step on the improved filterability and drying characteristics of form IV atorvastatin hydrate compared to the amorphous form. It must therefore be decided whether there was an incentive for the skilled person to arrive at the present solution in the expectation of achieving these improved characteristics.

As pointed out by the appellant, amorphous forms are generally known to be more soluble and have greater bioavailability than their crystalline counterparts. However, several disadvantages can also generally be expected for the amorphous form, namely, with respect to chemical and physical instability (see document (27), page 799, left-hand column and document (10), page 952, section entitled "Amorphous Forms").

In addition, the following is stated in document (28) (see page 527, left-hand column, first sentence):

"Crystalline products are generally the easiest to isolate, purify, dry and, in a batch process, handle and formulate."

Thus, in view of his general knowledge, as reflected in this excerpt from document (28), the skilled person, starting from the amorphous form of a pharmaceutically active compound as closest prior art, would have a clear expectation that a crystalline form thereof would provide a solution to the problem as defined under point 5.1 above. Although this might not be true of every crystalline form obtained (cf. document (28), page 527, left-hand column, second and third sentences), it was nevertheless obvious to try this avenue with a reasonable expectation of success without involving any inventive ingenuity.

The board cannot accept the appellant's contention that the skilled person would be dissuaded from attempting to obtain a crystalline form by the prospect of a potential loss of solubility and bioavailability when compared to the amorphous form. On the contrary, the skilled person would regard this as being a matter of trade-off between the expected advantages and disadvantages of these two classes of solid-state forms, as outlined above.

The appellant further argued that the presence of an inventive step was supported by the fact that a specific polymorph was being claimed rather than crystalline forms in general. The board does not deny

that there may be other options for solving the problem posed (see e.g. patent in suit, paragraph [0036]). However, an arbitrary selection from a group of equally suitable candidates cannot be viewed as involving an inventive step.

- 5.3 Therefore, the subject-matter of claim 3 of the main request and claim 1 of the auxiliary request represents an obvious solution to the problem posed and does not involve an inventive step.

Since a decision can only be taken on a request as a whole, none of the further claims need be examined.

Consequently, the appellant's main and auxiliary requests are rejected for lack of inventive step of claims 3 and 1, respectively.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

T. Buschek

P. Ranguis