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Datasheet for the decision of 29 June 2009

Case Number: T 0928/06 - 3.3.02

Application Number: 98908091.6

Publication Number: 0966287

IPC: A61K 31/55

Language of the proceedings: EN

Title of invention:
Oxacarbazepine film-coated tablets

Applicants/Patentees:
NOVARTIS AG, et al

Opponents:
TECNIMEDE SOCIEDADE TECNICO-MEDICINAL S.A.
Generics [UK] Limited
TARO PHARMACEUTICALS Inc

Headword:
Oxacarbazepine tablets/NOVARTIS AG, et al

Relevant legal provisions:
EPC Art. 101(2)(3)(b)

Relevant legal provisions (EPC 1973):
EPC Art. 56

Keyword:
"Main and auxiliary request - inventive step - no: obvious to try"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0928/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 29 June 2009

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 20 April 2006 concerning maintenance of European patent No. 0966287 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
T. Karamanli

Summary of Facts and Submissions

I. European patent No. 0 966 287, based on application No. 98 908 091.6, was granted on the basis of 10 claims.

Independent claims 1 and 9 as granted read as follows:

1. A formulation comprising oxacarbazepine having a median particle size of 2 to l2 µm, preferably 4 to 12 µm, more preferably 4 to 10 µm and with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2%.

9. Oxacarbazepine having a median particle size of 2 to l2 µm, preferably 4 to 12 µm, more preferably 4 to 10 µm.

II. Notices of opposition were filed against the granted patent by opponent 1 and appellant-opponents 2 and 3 (opponents 2 and 3).

The patent was opposed for lack of novelty and inventive step under Article 100(a) EPC 1973, insufficiency of disclosure (Article 100(b) EPC 1973) and added subject-matter (Article 100(c) EPC 1973).

The documents cited during the proceedings before the opposition division and the board of appeal included the following:

(4A/B) EP-A-646374/US-A-5472714
(5) DE-A-2011087
(7) M. Gibaldi in "Biopharmaceutics and Clinical Pharmacokinetics" 4th ed., Lea and Febiger, 1991, p.51

(22) Austria Codex, 1995/1996, p. 4372-4375
(24) Dam and Jensen, Antiepileptic drugs, 1989, Third Edition, Chapter 66:913-924
(Annex 3) International Journal of Clinical Pharmacology and therapeutics, Vol. 40, No. 11/2002, pages 524-532.

III. The appeal lies from the interlocutory decision of the Opposition Division maintaining the patent in amended form under Articles 102(3) and 106(3) EPC 1973 pronounced on 14 March 2006.

As to the objection under Article 123 EPC 1973, the Opposition Division observed that it was raised only against possible amendments.

The Opposition Division took the view that the subject-matter of claims 9 and 10 of the set of claims as granted (main request) was anticipated by the disclosure in, for instance, document (4A), which disclosed the product oxacarbazepine per se, because it considered that the subject-matter of those claims was not restricted by the feature relating to the median particle size.

Concerning the auxiliary request filed during the oral proceedings, which differed from the main request only in that claims 9 and 10 were deleted, the Opposition Division held that its subject-matter was novel vis-à-vis the available prior art because of the feature relating to the median particle size.

It moreover considered that this feature involved an inventive step vis-à-vis the closest prior art

represented by document (4A/B), because a particle size reduction would not systematically result in an enhanced bioavailability.

It further considered that the patent in suit, in particular examples 1 and 2, disclosed the subject-matter of the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art. In fact, the opponents' argument that there were difficulties in preparing the claimed particles related only to some specific techniques, so that this did not put sufficiency into question.

IV. The appellant-patent proprietors and the appellant-opponents 2 and 3 (opponents 2 and 3) lodged an appeal against the said decision and filed arguments.

Opponent 1, which did not appeal, is respondent.

V. With its letter dated 27 May 2009, appellant opponent O3 informed the Board that it would not be attending the oral proceedings.

VI. In the communication of 15 June 2009, the Board expressed its preliminary unfavourable opinion as to inventive step.

VII. Oral proceedings were held before the Board on 29 June 2009.

VIII. The submissions of the appellant-patent proprietors during the oral proceedings can be summarised as follows:

In its view, the reduction of the particle size of oxacarbazepine to a median particle size according to claim 1 of the patent in suit (i.e. micronisation grade) solved three different problems, namely the problem of enhancing the bioavailability of the drug, increasing compliance and increasing colour stability.

The micronisation of oxacarbazepine was not obvious because the skilled person would be deterred from taking this measure for five main reasons:

There are instances in which particle size reduction fails to increase the adsorption rate, for example when dissolution is not the rate limiting factor, when the therapeutic drug is absorbed independently of its particle size, or when the drug particles aggregate, which then leads to a decrease in surface area.

Since solubility and dissolution rate do not increase ad infinitum as particle size is reduced, the skilled person might believe that the optimum particle size was already achieved in the prior art document (4A/B), so that he had no reason to micronise the prior art particles.

Micronisation is a technique requiring special equipment and special safety measures for the technicians, so that the skilled person would not take such a measure unless fairly sure of the outcome.
As reduction of the particle size would decrease the stability of the drug, the skilled person would be reluctant to take such a measure.

Since the drug under consideration is a drug used in the treatment of epilepsy, which requires that the dosage be strictly respected to be efficient, the skilled person would not dare to take any risk in changing the formulation, unless sure in advance that the dosage was not affected.

Finally, the appellant-patent proprietors submitted that since the drug was already known in 1969, as was apparent from document (5), a long time was elapsed before the present invention was made, which indicated that the claimed subject-matter was not obvious.

In addition, as to the subject-matter of claims 9 and 10 of the main request (set of claims as granted), it contested, in its grounds of appeal, the Opposition Division's analysis that the feature relating to the median particle size should not be taken into account when assessing novelty of these claims.

IX. The submissions of the appellant-opponents (opponents O2 and O3) and of the respondent (opponent 01) can be summarised as follows:

They argued that it was a general rule and common general knowledge in the field of pharmaceutical drug formulation that bioavailability of a substance was affected by its particle size since this would increase the drug's surface area, thus increasing its solubility which directly influence the rate and extent of gastro-intestinal adsorption.

In their opinion, the presence of a few exceptions would not hide this general rule and any formulation

scientist would in any case investigate, as a matter of routine, the effect of a drug's particle size on its bioavailability using conventional techniques such as micronisation.

They also contended that the increased bioavailability was not demonstrated in the contested patent and that comparative examples provided by the proprietors were inappropriate to that end.

They also observed that no data at all were provided in either the patent in suite or the file to substantiate the proprietor's statement that an improved stability was also achieved.

In addition, appellant-opponent 2 argued, in its grounds of appeal, that the feature relating to the median particle size should not be taken into account when assessing novelty, so that claim 1, which thus related to a compound *per se*, was anticipated by the disclosure in document (4A/B).

X. With a letter dated 19 March 2007 the appellant-patent proprietors requested "to maintain the patent as granted (main request as substantiated in the appeal by the proprietors) and to maintain the patent in amended form on the basis of the documents considered allowable by the Opposition Division (auxiliary request)".

In the oral proceedings the Board explained to the patentees that their auxiliary request is to be interpreted as a request for dismissal of the appeals of the opponents 2 and 3. The patentees did not object to this.

The appellant-opponents 2 and 3 and the respondent requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the decision

1. The appeal is admissible.

2. Claims of the patent as granted

2.1 Article 100(b) EPC 1973

During the appeal proceedings the appellant-opponents did not raise any objections under Article 100(b) EPC 1973 and the Board sees no reason to differ from the favourable conclusions of the Opposition Division in that respect (Opposition Division's decision, page 6, point 3).

2.2 Novelty (Articles 100(a) and 54(1) EPC 1973)

The Board agrees with the favourable conclusions of the Opposition Division as to novelty of claim 1 (Opposition Division's decision, pages 6 and 7, point 4.1).

In that respect, the Board does not share appellant-opponent 2's argument that the feature relating to the median particle size should not be taken into account when assessing novelty. However, in the light of the results of the assessment of inventive step, there is no need to develop this further.

2.3 Inventive step (Articles 100(a) and 56 EPC 1973)

2.3.1 The contested patent relates to an oxacarbazepine formulation having a median particle size of 2 to l2 µm with a maximum residue on a 40 µm sieve of up to 5%, e.g. 2% (page 2, paragraph 6).

The Board considers that document (4B), which discloses a conventional oxacarbazepine formulation, represents the closest prior art (Example 1).

According to the description of the patent in suit, the claimed formulation enhances bioavailability and increases compliance and colour stability.

During the oral proceedings, the appellant-patent proprietor, referring to document (22), an extract of the Austrian codex for pharmacists, submitted that it was well-known in the field relating to this drug that the treatment required intake of the drug with meals to increase its bioavailability.

As to the effect on colour stability, the Board observes, as objected by the appellant-opponents and the respondent, that this alleged effect is not at all substantiated, either in the patent itself or in the file.

Moreover, the Board notes that the amount of iron oxide, an agent used to achieve colour stability, in the examples of the patent and in the example of document (4B) is similar.

As to the effect relating to bioavailability and compliance, the Board considers, in favour of the appellant-patent proprietors, that this is confirmed by the results published in annex 3 filed during the appeal proceedings, which shows that a formulation according to claim 1 has an increased bioavailability so that it can be taken with or without food.

Accordingly, vis-à-vis document (4B), the technical problem can therefore only be formulated as the provision of a formulation of oxacarbazepine with increased bioavailability so that it can be taken at any time.

2.3.2 This problem is solved by the use of a formulation having the technical features of claim 1.

In the light of results published in Annex 3 filed with the appellant-opponent's 2 statement of grounds of appeal, the Board is satisfied that the problem has been solved (page 532, last paragraph).

2.3.3 Thus the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

Document (4B) discloses only the average particle size of the compacted product, i.e. 400 µm, so that no information is available concerning the actual particle size before compaction. However, as this document does not mention any particular method of preparation, the Board has no reason to doubt, as argued by the appellant-patent proprietors, that example 1 of document (4B), which corresponds to its own previously

marketed product Trileptal®, was prepared by a conventional method (i.e. not by micronisation), and has a median particle size well above 2 to l2 µm, namely 50 to 70 µm as accepted by the Opposition Division.

Having regard to document (7) for instance (page 51, left column, third paragraph), it appears that there is indeed a general teaching that the drug dissolves more rapidly, which results in a more rapid and complete absorption - conditions which increase the bioavailability - when its surface area is increased, so that poorly soluble or slowly dissolving drugs are micronized in order to reduce the particle size of the drug (page 51, left column, third paragraph).

Indeed, it is also known, for instance from document (24), that oxcarbazepine is a drug having a very low solubility in water (see e.g. (24), page 913, right column, first paragraph).

Accordingly, the skilled person would arrive at the claimed subject-matter in order to solve the above defined problem without inventive step, merely by following the clear teaching provided in document (7).

Accordingly, the subject-matter of claim 1 does not fulfil the requirements of inventive step.

2.3.4 The Board agrees with the appellant-patent proprietors' submission that there are instances in which particle size reduction fails to increase the adsorption rate, for example when dissolution is not the rate-limiting factor, when the therapeutic drug is absorbed

independently of its particle size, or when the drug particle aggregates, which then leads to a decrease in surface area. The mere fact that there are singular examples which do not work, does not however put the general application of this teaching into question, so that the Board remains convinced that the skilled person would not be deterred from trying for this reason. The more so, since it has no reason to believe that the present drug would belong to such exceptions.

Again, the Board agrees that solubility and dissolution rate do not increase ad infinitum as particle size is reduced. The skilled person however had no reason to believe that the optimum particle size was already achieved in the prior art. The more so since the prior art particles were not micronized so that he knew that this possibility was left open. Accordingly, the Board remains convinced that any formulation scientist would optimize, as a matter of routine, the effect of a drug's particle size on its bioavailability using conventional techniques such as micronisation.

As to the argument that micronisation is a technique requiring special equipment and special safety measures for the technicians, the Board observes that this argument is not relevant since the problems mentioned by the appellant-patent proprietors arise only when it comes to the product's industrial preparation i.e. after the skilled person would have already realized through experimentation in the laboratory that micronisation was the right solution.

The Board also shares the appellant-patent proprietors' opinion that, as reduction of the particule size would

decrease the stability of the drug, the skilled person would be reluctant to take such a measure. This would however in no case deter him from trying a promising solution. In fact, the Board is convinced that when comparing, on the one hand, the hope of improving bioavaililty and, as a result, compliance, with, on the other, a possible risk of discolouration, the skilled person would always decide for the patient's comfort rather than for the aesthetic aspect of the medicament.

Nor can the last argument presented by the appellant-patent proprietors succeed. It is indeed correct that the drug under consideration is used in the treatment of epilepsy, which requires that the dosage be strictly respected to be efficient. Any epilepsy treatment however as a rule requires that the patient be tested at the beginning of the treatment to determine the optimal drug amount in the blood. The skilled person would therefore not be deterred from trying a promising new formulation.

Finally, as to the appellant-patent proprietors' submission concerning the long time which elapsed before the present invention was made, which would indicate that the claimed subject-matter was not obvious, the Board would like to stress that this aspect could only confirm a favourable objective assessment of inventive step but cannot replace it.

Concerning the stability aspect, the Board would like to add that, even if an effect had been shown, this would not change its unfavourable conclusions as to inventive step since the skilled person would in any case have taken the measure of reducing the particle

size to increase the bioavailability so that a supplementary effect could only be regarded a bonus for which no inventive step can be acknowledged.

Accordingly, the Board's conclusions under 2.3.3 remain unchanged.

Under these circumstances, there is no need to consider the remaining claims.

3. Claims of the patent as maintained in amended form by the first instance

Since claim 1 of this set of claims is identical to claim 1 of the patent as granted, the above conclusions apply also to this set of claims.

4. Conclusion

Since the ground for opposition under Article 100(b) EPC 1973 (lack of inventive step) prejudices the maintenance of the patent as granted and since, taking into consideration the amendments made by the patent proprietors, the patent and the invention to which it relates do not meet the requirements of the EPC, the patent must be revoked (Article 101(2) and (3)(b) EPC).

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar The Chairman

N. Maslin U. Oswald