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Datasheet for the decision of 15 July 2009

Case Number: T 0311/07 - 3.3.02

Application Number: 99908594.7

Publication Number: 1066027

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition of topiramate

Patentee:
Ortho-McNeil Parmaceutical, Inc.

Opponent:
TECNIMEDE SOCIEDADE TECNICO-MEDICINAL S.A.

Headword:
Pharmaceutical composition of Topiramate/ORTHO-McNEIL PHARMACEUTICAL, INC.

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and first and second auxiliary requests: Inventive step (no): Use of a coating for masking the bitter taste of Topiramate obvious"
"Second auxiliary request: admissibility (yes): Amendments only concerned deletion of claims"

Decisions cited:
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Catchword:
-

Case Number: T 0311/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 15 July 2009

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 19 December 2006 rejecting the opposition filed against European patent No. 1066027 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 1 066 027 based on application No. 99 908 594.7 was granted on the basis of a set of 10 claims.

The independent claims read as follows:

"1. A process for forming a pharmaceutical composition comprising:

(a) preparing core particles comprising an active agent of topiramate;

(b) drying the core particles from step (a) to form dried core particles;

(c) coating the dried core particles from step (b) with a taste masking mixture to form coated particles; and

(d) drying the coated particles from step (c) to form the pharmaceutical composition wherein the amount of
taste masking mixture ranges from 7% by weight to 15% by weight of the pharmaceutical composition.

5. A pharmaceutical composition comprising

(a) core particles containing an active agent of topiramate, wherein the core particles have an initial particle size between 0.100 mm and 2.5 mm; and

(b) a taste mask coating, wherein the taste mask coating comprises between 7% by weight and 15% by weight of the pharmaceutical composition and wherein the coated particles of the pharmaceutical composition have a final particle size of 0.100 mm to 2.5 mm.

9. A pharmaceutical composition comprising 85 to 93% by weight core beads, and 7 to 15% by weight of a coating; wherein the core beads comprise 18 to 21% by weight of topiramate, 8 to 11% by weight of povidone, and 58 to 61% by weight of sugar spheres; and the coating comprises 6 to 9% by weight of cellulose acetate, and 2 to 5% by weight of povidone.

10. Use of a composition according to Claims 5 to 9 in the preparation of a medicament for treating diabetes, convulsions in a mammal or epilepsy in a mammal."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and lack of inventive step.

III. The documents cited during the opposition and appeal proceedings included the following:

(l) WO 88/03795 Al
(2) Isaac Ghebre-Sellassie, Multiparticulate Oral Drug Delivery, 1994, p.65
(5) EP-A-0 138 441
(11) Handbook of Pharmaceutical Excipients (2nd Edition, 1994), p. 510-511
(15) US-A-4 851 226
(16) EP-A-0 459 695
(17) EP-A-0 317 274

IV. In the decision pronounced on 21 November 2006, the opposition division rejected the opposition. The opposition division did not admit insufficiency of disclosure as new ground of opposition into the opposition proceedings. The subject-matter of the claims as granted was found to be novel and to involve an inventive step. As regards inventive step, the problem with regard to document (5), which had been identified as closest prior art, was defined as the provision of a pharmaceutical composition comprising topiramate having satisfactory taste masking, the desired release/bioavailability properties as well as moisture stability. As none of documents (1), (15), (16) or (17) addressed this problem for the simple reason that topiramate was not mentioned therein, the skilled person had no reason to combine the teaching of document (5) with the teaching of documents (1), (15), (16) or (17). As a consequence, the subject-matter of the claims as granted involved an inventive step.

V. The appellant (opponent) lodged an appeal against that decision.

VI. In the statement of the grounds of appeal of 18 April 2007, the appellant raised objections under Article 56 EPC.

VII. In his reply to the statement of the grounds of appeal dated 7 September 2007, the respondent (patentee) submitted counter arguments and declared that the auxiliary request filed with his letter of 20 September 2006 (= first auxiliary request) was maintained.

Claim 1 of the first auxiliary request reads as follows:

"1. A process for forming a pharmaceutical composition comprising:

(a) preparing core particles comprising an active agent of topiramate;

(b) drying the core particles from step (a) to form dried core particles having a particle size of 0.100 mm to 2.5 mm;

(c) coating the dried core particles from step (b) with a taste masking mixture to form coated particles; and

(d) drying the coated particles from step (c) to form the pharmaceutical composition wherein the amount of
taste masking mixture ranges from 7% by weight to 15% by weight of the pharmaceutical composition and the coated particles have a final particle size of 0.100 mm to 2.5 mm."

Independent claims 5, 9 and 10 are identical to claims 5, 9 and 10 of the main request.

VIII. Oral proceedings took place on 15 July 2009. At the oral proceedings, the respondent filed a second auxiliary request, wherein independent claim 1 is identical to claim 9 of the main request. Claim 2 corresponds to claim 10 of the main request, except that the back reference was changed from "…according to claims 5 to 9" to "…according to claim 1".

IX. The appellant's arguments can be summarised as follows:

No further arguments were submitted in connection with novelty. As regards inventive step, either document (16) alone or the combination of document (5) with any one of documents (15), (16) or (17) was considered to render the claimed subject-matter obvious. No objections were raised in connection with the admissibility of the second auxiliary request.

X. The respondent's arguments can be summarised as follows:

Document (16) did not mention topiramate and did therefore not constitute the closest prior art. The present invention involved an inventive step, as it was concerned with the provision of pharmaceutical compositions where the unpleasant taste of topiramate was effectively masked and which were more stable than the compositions of the prior art. To be specific, the compositions comprising individually coated particles were more stable than coated tablets. In addition, the compositions of the present inventions could be sprinkled onto food.

XI. The appellant requested that the decision under appeal be set aside and that the European patent be revoked.

The respondent requested that the appeal be dismissed or in the alternative that the patent be maintained on the basis of the first or second auxiliary requests.

Reasons for the Decision

1. The appeal is admissible.

2. Main request:

2.1 Novelty:

The appellant did not submit any arguments in the course of the appeal procedure. The board concurs with the finding of the opposition division that the subject-matter of the main request is novel over document (1), as document (1) does not specifically disclose topiramate. As a consequence, the requirements of Article 54 EPC are met.

2.2 Inventive step of claim 5:

2.2.1 The present invention concerns the provision of palatable and stable solid formulations of topiramate for use in patients having difficulties swallowing tablets or capsules (see paragraph [0008] of the contested patent).

2.2.2 Document (5) constitutes the closest prior art. It discloses oral dosage forms, preferably tablets or capsules, comprising a sulfamate, which, in a preferred embodiment, includes 2,3 : 4,5-bis-0-(1-methyl-ethylidene)-ß-D-fructopyranose sulfamate (= topiramate) (see page 8, lines 14-17; claims 1, 6 and 9; example 3). Document (5) does not mention the bitter taste of topiramate, but the board concurs with the opinion of the opposition division that this property of topiramate is known to the skilled person and, as a

consequence, is part of his common general knowledge (see point 3.2.1 of the opposition division's decision).

Starting from this prior art, the technical problem has to be formulated as follows: provision of a topiramate comprising pharmaceutical composition, which can be easily swallowed, which does not taste bitter and which is more stable. The problem was solved by a composition as defined in claim 5, i.e. by a composition, wherein topiramate containing core particles with an initial particle size between 0.100 to 2.5 mm are coated with between 7 to 15% by weight of a taste mask coating so that the final particle size of the coated particles is between 0.100 to 2.5 mm.

2.2.3 As regards the enhanced stability, it may be argued that the stability tests disclosed in the contested patent (see paragraphs [0041] to [0044] as well as tables 2 and 4), which involve specific coatings comprising cellulose acetate and PVP, are not representative for any taste mask coating as mentioned in claim 5. However, the board concludes that a taste mask coating completely surrounds the active agent, thus forming a barrier which not only prevents contact of the active agent with the oral cavity, but also protects it from interaction with the environment in general, including interaction with moisture or light. In the light of this finding, the board is satisfied that the problem defined above was plausibly solved, even though the stability tests in the contested patent are not representative for the entirety of the taste mask coatings.

2.2.4 The skilled person trying to solve the above-mentioned problem would turn to document (15). This document discloses chewable tablets for persons having trouble swallowing whole tablets comprising compressed particles comprising an active agent having a disagreeable taste, wherein the individual particles are coated with a blend of cellulose acetate and polyvinyl pyrrolidone (PVP) for masking the unpleasant taste of the active agent (see column 1, lines 19-23, 31-33 and 63-68; column 2, lines 3-15). Preferably, the coating constitutes about 5-20% by weight of the particle, wherein 12 and 15% by weight are particularly preferred (see tables I to XIV) and the active agent is acetaminophen (see column 5, lines 22-28). However, other active agents such as ibuprofen and loperamide HCl are also used (see column 7, lines 12-15). The preferred particle size of acetaminophen and ibuprofen is about 60 mesh (see column 6, lines 45-46 and column 7, lines 12-13) and 40-60 mesh for loperamide HCl (see column 7, lines 14-15). As a consequence, the teaching of document (15) relates to compositions comprising all the features of claim 5 of the present main request except for the selection of topiramate as bitter tasting active agent.

The skilled person is aware that the taste masking activity of the coating, which in document (15) is demonstrated for acetaminophen, ibuprofen and loperamide HCl, also works for other active agents characterised by a bad taste, such as topiramate. After all, the taste masking effect of the coating is obtained by creating a physical barrier around the active agent and thereby preventing any contact between the active agent and the oral cavity, which is *a priori*

independent of the pharmacological activity or any other properties of the active agent.

It is noted that the document (15) does not mention an enhanced stability of the coated particles. However, in the light of the reasoning developed in paragraph 2.2.3 above, the board came to the conclusion that such a stabilising effect was obvious for the skilled person. Reference is also made to document (2), which, in connection with multiparticulate oral drug delivery systems, states that film coating is used to mask taste, to reduce odour or to stabilise moisture-sensitive products (see page 65, last full paragraph).

2.2.5 As a consequence, the subject-matter of claim 5 is rendered obvious by document (5) in combination with document (15). The requirements of Article 56 EPC are therefore not met.

In the light of this finding, an assessment of inventive step of the further independent claims is not necessary.

3. First auxiliary request - inventive step of claim 5:

Claim 5 of the first auxiliary request is identical to claim 5 of the main request. As a consequence, the reasoning developed in point 2.2 above also applies to claim 5 of the first auxiliary request. The requirements of Article 56 EPC are therefore not met.

In the light of this finding, an assessment of inventive step of the further independent claims is not necessary.

4. Second auxiliary request:

4.1 Admissibility:

The second auxiliary request was only filed at an advanced stage of the oral proceedings. However, the amendments only concern the deletion of claims 1 to 8 as granted. Moreover, such amendments were already announced in the letter of 7 September 2007. As a consequence, the second auxiliary request was admitted into the proceedings (Article 13(1) RPBA).

4.2 Claim 1 - inventive step

4.2.1 The pharmaceutical composition of claim 1 now comprises
(a) 85 to 93% by weight core beads, and
(b) 7 to 15% by weight of a coating;

the core beads comprise
(c) 18 to 21% by weight of
(d) topiramate,
(e) 8 to 11% by weight of povidone, and
(f) 58 to 61% by weight of sugar spheres;

the coating comprises
(g) 6 to 9% by weight of cellulose acetate, and
(h) 2 to 5% by weight of povidone.

4.2.2 The pharmaceutical composition of present claim 1 is a preferred embodiment of the compositions claimed in the previous requests. In view of the fact that the claimed composition is defined by a large number of technical features, it is first necessary to identify those

features that are related to the technical problem that the contested patent intends to solve. As was already mentioned in point 2.2.1 above, the present invention concerns the provision of palatable and stable solid formulations of topiramate for use in patients having difficulties swallowing tablets or capsules. In view of this problem, the board concludes that, except for the fact that the core beads comprise the bitter tasting topiramate, their composition is *a priori* not related to the technical problem, which was solved by the provision of a taste mask coating. There is no evidence that core beads in which 18-21% by weight of topiramate is coated onto sugar spheres in the presence of PVP are more beneficial in terms of taste masking or stability than core beads composed of conventional granules. As a consequence, features (c), (e) and (f) as defined in point 4.2.1 above cannot be taken into consideration in the subsequent assessment of inventive step. For completeness sake, it is noted that the use of sugar spheres as inert cores in tablet and capsule formulation is well known (see document (11)).

4.2.3 As far as the features (a), (b), (d), (g) and (h) are concerned, it is noted that features (a), (b) and (d) are already present in the composition defined in claim 5 of the previous requests. It therefore has to be established whether the additional features (g) and (h) are able to establish an inventive step over the combination of documents (5) and (15). In this context, reference is made to the passage in column 4, lines 52-55 of document (15), which indicates that the coating is preferably a blend containing about 80 to 97% of cellulose acetate by weight of the coating, the remainder being PVP. When rapid release of the

medicament is desired, the blend contains 80-88% by weight of cellulose acetate and 12-20% by weight of PVP (see column 4, lines 58-60). As the coating constitutes about 5-20% of the total dry weight of the coated particle (see column 5, lines 22-28), the calculated content of cellulose acetate in the particles is 4-19.4% by weight (4-17.6% in case of rapid release) and 0.15-4% by weight (0.6-4% by weight in case of rapid release) for PVP. These ranges considerably overlap with the concentration ranges of present claim 1. Moreover, in several of the examples (see tables II, XI and XII) the particles comprise 9.6% by weight of cellulose acetate and 2.4% by weight of PVP. There is no evidence that the selection of 6-9% by weight (present claim 1) out of 4-17.6% by weight (document (15)) of cellulose acetate yields any non-obvious effects.

4.2.4 As a consequence, the reasoning developed in point 2.2 above applies *mutatis mutandis* to claim 1 of the second auxiliary request. As a consequence, the requirements of Article 56 EPC are not met.

In the light of this finding, an assessment of inventive step of independent claim 2 is not necessary.

4.3 Further arguments of the respondent:

4.3.1 In the written procedure, it was reasoned that the present invention involved an inventive step, as the pharmaceutical compositions of the contested patent were not only characterised by effective taste masking properties and enhanced stability, but also by good

bioavailability (see also paragraph [0008] of the contested patent).

This argument cannot succeed, as document (15) also relates to rapid release compositions, which can be obtained by choosing a relatively high proportion of PVP (see column 4, lines 58-63). In this context, it is noted that for the water soluble topiramate, dissolution is considered to be equivalent to bioavailability (see page 2 of the respondent's letter dated 7 September 2007, paragraph "bioavailability").

4.3.2 Stability tests revealed that individually coated beads according to the present invention were more resistant to moisture than TOPAMAX tablets, where the tablet as a whole rather than the individual particles were coated.

It is noted that the stability tests of the contested patent (see point 2.2.3 above) are considered to be representative of the subject-matter of claim 1 of the second auxiliary request where, in contrast to the previous requests, the coating now mandatorily comprises cellulose acetate and PVP. However, the skilled person providing for a topiramate containing pharmaceutical composition, which can be easily swallowed, which does not taste bitter and which is more stable than the compositions of document (5) (see point 2.2.2 above) would for the reasons outlined in points 2.2.3, 2.2.4 and 4.2.3 above choose a pharmaceutical composition comprising individually coated particles as claimed in present claim 1. The fact that these individually coated particles are additionally more resistant to moisture can only be regarded as a bonus effect, which is not able to

establish an inventive step. It is additionally emphasised that document (2) mentions that coating of individual particles stabilises moisture-sensitive products. As a consequence, this argument cannot succeed, either.

4.3.3 The compositions of the present invention could be sprinkled onto food. None of documents (5) or (15) to (17) related to this property.

This feature is not included in the subject-matter as claimed, which includes chewable tablets as disclosed in document (15). As a consequence, this argument cannot be taken into consideration.

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:

N. Maslin U. Oswald