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Datasheet for the decision of 7 October 2024

Case Number: T 2930/19 - 3.3.07

Application Number: 10196245.4

Publication Number: 2308466

IPC: A61K9/00, A61K47/02, A61K47/10, A61K31/535, A61K31/5575

Language of the proceedings: EN

Title of invention:
Aqueous pharmaceutical compositions containing borate-polyol complexes

Patent Proprietor:
NOVARTIS AG

Opponents:
Generics [UK] Limited (trading as Mylan)
Alfred E. Tiefenbacher (GmbH & Co. KG)

Headword:
Aqueous pharmaceutical compositions containing borate-polyol complexes / NOVARTIS

Relevant legal provisions:
RPBA 2020 Art. 12(4)
EPC Art. 54(3), 56, 87(1), 123(2), 76(1)

Keyword:

Amendment to appeal case - amendment overcomes issues raised (yes)
Amendments - added subject-matter (no)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:

G 0001/22

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Boards of Appeal

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Case Number: T 2930/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 October 2024

Appellant: (Opponent 1)	Generics [UK] Limited (trading as Mylan) Building 4, Trident Place Mosquito Way, Hatfield GB-Hertfordshire AL 10 9UL (GB)
Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Appellant: (Opponent 2)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Respondent: (Patent Proprietor)	NOVARTIS AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 September 2019 concerning maintenance of the European Patent No. 2308466 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
A. Jimenez

Summary of Facts and Submissions

I. The appeals were filed by both opponents, and, initially, by the patent proprietor, against the interlocutory decision of the opposition division finding that, on the basis of auxiliary request 2, the patent met the requirements of the EPC.

II. The decision was based on the patent as granted as the main request, and on two auxiliary requests.

Claim 1 of the main request related to a multi-dose ophthalmic composition, comprising among other components:
- at least 0.25 but less than 1.5 w/v % of a first polyol being mannitol, and
- at least 0.25 w/v % but less than 0.5 w/v % of a borate.

In claim 1 of auxiliary request 1, the upper limit for the amount of borate was amended to less than 0.35 w/v %. Claim 1 of auxiliary request 2 additionally specified the presence of HCO-40 as a surfactant.

III. The opposition division decided that:

(a) The combination, in claim 1 of the main request, of the ranges for the first polyol and borate amounts infringed Articles 123(2) and 76(1) EPC.

(b) The priority was invalid in respect of auxiliary request 1, with the consequence that D14 (WO 2009/117316) was part of the prior art under

Article 54(3) EPC and anticipated the claimed subject-matter.

(c) Auxiliary request 2 complied with the criteria of Articles 123(2) and 76(1) EPC. Its subject-matter enjoyed a valid claim to priority and was novel. D7 (WO 2005/060953) represented the closest prior art, and not D6 (product label of Travatan® Z). Starting from D7, the claimed subject-matter involved an inventive step.

IV. In appeal, the patent proprietor initially defended their case on the basis of the patent as granted (main request), auxiliary request 1 filed on 27 January 2020 with their statement setting out the grounds of appeal, auxiliary request 2 considered by the opposition division, and auxiliary requests 3-13 filed on 9 June 2020 with their reply to the opponents' appeal.

In particular, claim 1 of **auxiliary request 5** read as follows:

"A multi-dose ophthalmic composition, comprising:
first polyol, the first polyol being mannitol, wherein the first polyol is at least 0.25 but less than 0.5 w/v % of the composition;
second polyol, the second polyol being propylene glycol wherein the second polyol is at least 0.1 but less than 5 w/v % of the composition;
borate, wherein the borate is at least 0.25 w/v % of the composition but less than 0.35 w/v % of the composition;
antimicrobial preservative wherein the preservative is at least 0.0003 but less than 0.003 w/v % of the composition and wherein the preservative is a polymeric quaternary ammonium compound;

travoprost; and
water;
wherein the pH of the composition is from 6.4 to 7.2."

The patent proprietor further filed the following document during the appeal proceedings:

D33: Wikipedia entry for tricine dated 8 June 2008

V. The Board issued summons to oral proceedings scheduled for 27 October 2022. These oral proceedings were then cancelled in view of the potential relevance of referral G 1/22 and G 2/22 (as explained in a communication dated 18 May 2022). The Board issued new summons to oral proceedings scheduled for 7 October 2024.

VI. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VII. By letters dated 15 August 2024, both opponents withdrew their requests for oral proceedings.

Oral proceedings were held before the Board in the presence of the patent proprietor only. During the oral proceedings, the patent proprietor withdrew their appeal and made auxiliary request 5 their main and sole request.

VIII. The parties' final requests were the following:

(a) Both appellants (opponent 1 and opponent 2) requested that the decision under appeal be set aside and that the patent be revoked.

(b) The respondent (patent proprietor) requested the maintenance of the patent on the basis of auxiliary request 5 filed on 9 June 2020 with the reply to the opponents' appeals.

IX. During the appeal proceedings, the appellants did not take position on the respondent's requests filed on 9 June 2020, including the sole remaining auxiliary request 5. The appellants had raised, in respect of previous requests in appeal, objections of:
- added subject-matter (Articles 123(2) and 76(1) EPC) against the mannitol range of 0.25-1.5 w/v %, and its combination with the borate range,
- invalidity of the priority, and consequently lack of novelty over D14, and
- lack of inventive step starting either from D7 or from D6 as closest prior art.

X. The respondent's argument may be summarised as follows:
- in auxiliary request 5, the mannitol upper and lower limits were the most preferred values recited on page 7, lines 10-12 of the application as filed;
- the priority was valid, because the choice of travoprost as the therapeutic agent was disclosed as preferred in the priority application. Hence, the claimed subject-matter was novel;
- starting from D6, the subject-matter of claim 1 differed by (i) the use of mannitol instead of sorbitol, (ii) the lower amount of borate (iii) the concentration of polymeric quaternary ammonium compound, and (iv) the higher pH. The problem was to provide a multi-dose pharmaceutical formulation of travoprost with better anti-microbial activity than the prior art, whilst retaining low toxicity, and improving buffering capacity. The claimed solution involved an inventive step, among others because the skilled person

would not raise the pH from 5.7 to within 6.4 to 7.2. The same conclusion would apply starting alternatively from D7.

Reasons for the Decision

1. Admittance

1.1 The present decision is based on the respondent's main and sole request, filed as auxiliary request 5 on 9 June 2020 with the respondent's reply to the opponents' appeals. This request is identical to auxiliary request 3 filed in the first instance proceedings, but does however not belong to the requests on which the decision under appeal was based, because the opposition division allowed a higher-ranking request.

Accordingly, under Article 12(4) RPBA, the present request is a part of the respondent's appeal case which "is to be regarded as an amendment, unless the party demonstrates that this part was admissibly raised and maintained in the proceedings leading to the decision under appeal. Any such amendment may be admitted only at the discretion of the Board."

1.2 In the assessment pursuant to Article 12(4) RPBA, a first step may be to determine whether the request was admissibly raised and maintained in the proceedings leading to the decision under appeal, and whether the party "demonstrates" this. If not, the request is to be regarded as an amendment to the party's appeal case and the Board will decide on its admittance in a second step of the assessment.

However, the examination as to whether the request is to be regarded as an amendment, and is hence subject to the Board's discretion, is not necessary if the Board finds that this exercise of discretion would in any case lead to the admittance of the request.

In the present case, it follows from the reasoning set out below and the Board's present decision to allow the main request, that this request is suitable to address the issues which led to the decision under appeal, in particular with respect to added subject-matter. The amendments to the respective ranges for mannitol and borate were the topic of debate during the first instance proceedings already and do no raise complex issues. In addition, the Board considers that the absence of objection by the appellants against the admission of the present request, while not being sufficient or excluding the Board's *ex officio* exercise of discretion, may be considered in the exercise of discretion under Article 12(4) RPBA together with the non-exhaustive list of criteria recited therein.

1.3 Accordingly, the Board admitted the main request.

2. Articles 123(2) and 76(1) EPC

2.1 The patent in suit derives from a divisional application. For the following reasons, the Board concludes that the main request meets the requirements of both Article 123(2) EPC (see 2.2 below) and Article 76(1) EPC (see 2.3).

2.2 Regarding firstly the question of added subject-matter under Article 123(2) EPC, claim 1 of the main request combines the features of claims 1, 10, 11, 13 and 14 of

the divisional application as filed with additionally the following amended ranges:

(a) the range for the amount of the first polyol being mannitol, namely at least 0.25 but less than 0.5 w/v % of the composition, combines the narrowest lower and upper limits recited, for the first polyol in general, on page 7, lines 8-12 of the divisional application as filed. Since mannitol is the preferred first polyol, the above passage unambiguously applies to the first polyol being mannitol;

(b) likewise, the range for the amount of borate, namely at least 0.25 but less than 0.35 w/v % of the composition, combines the narrowest lower and upper limits recited in the paragraph bridging pages 7 and 8.

In the Board's view, these respective upper and lower limits would be understood by the skilled reader to be preferred, considering that they are not only stated to be the most "typical" values in the above passages but also that they are the narrowest and come closest to the preferred exemplary formulation of table A on page 12. The divisional application as filed thus contains a pointer to the claimed combination.

The appellant's objections of added subject-matter in appeal were directed at the mannitol upper limit of 1.5 w/v % isolated from page 18 of the divisional application as filed, and at a borate range of 0.25-0.50 w/v %, none of which applies to the present amended request.

Accordingly, the main request fulfils the requirements of Article 123(2) EPC.

2.3 The discussion of added subject-matter over the parent application as filed is identical in respect of the above two ranges, since the parent and divisional applications as filed contain the same description. Accordingly, the criteria of Article 76(1) EPC are also met.

3. Priority and Novelty

3.1 The patent claims priority from the earlier application D20 (US 61/037137) filed on 17 March 2008.

3.1.1 The appellants do not challenge the opposition division's finding that the applicant is entitled to claim priority from D20 (see the appealed decision, §4.1). In view of the rebuttable presumption of entitlement to claim priority established by decision G 1/22, the Board sees no reason to depart from this conclusion.

3.1.2 The Board furthermore finds that the main request relates to the same invention as the priority application D20.

Regarding the ranges 0.25-0.5 w/v % for mannitol and 0.25-0.35 w/v % for borate, and their combination, the priority application D20 contains the same relevant passages as the divisional and parent applications as filed (see page 7, lines 9-13 and 31-37), such that the same conclusion as to disclosure applies.

Furthermore, and contrary to the appellants' view, the combination of these features with the choice of

travoprost as the therapeutic agent does not add subject-matter. The general use of travoprost is disclosed as one alternative in the list on page 10 (lines 12-19), and the fact that all examples include travoprost can be considered as a pointer to this selection, i.e. as an indication that travoprost is preferred.

3.2 Considering that the main request enjoys a valid claim to the priority date of 17 March 2008, the published patent application D14, whose earliest claimed priority date is also 17 March 2008, is not prejudicial to novelty under Article 54(3) EPC.

Hence the criteria of novelty are met.

4. Inventive step

4.1 The patent aims at improving preservation of aqueous multi-dose ophthalmic pharmaceutical compositions without increasing the potential for toxicity and while minimizing the resistance of the compositions to normalization of tear pH after application (see paragraphs [0002], [0003], [0008], [0010], [0012] and [0013]). To solve these problems, the proposed solution is to use two or more polyols in the presence of borate as claimed, so as to achieve desired buffering and anti-microbial activities (see paragraph [0017]). The claimed composition comprises a therapeutic agent which, in the granted patent, is selected to be travoprost.

The appellants raised objections of lack of inventive step starting either from Travatan® Z (D6) or from D7.

4.2 Starting from D7

4.2.1 D7 relates to a similar purpose as the patent in suit, namely enhanced antimicrobial activity in aqueous ophthalmic compositions without increasing the potential for toxicological effects (see page 3, lines 16-19; page 11, lines 16-22). According to D7 (page 8, lines 17-25), the organic buffers described therein may be included in various types of ophthalmic compositions, including not only solutions for treating contact lenses but also topical compositions used in the treatment of glaucoma. In the Board's view, considering its similar underlying technical problems and broad applicability, D7 is not disqualified as a suitable starting point for the assessment of inventive step by the lack of specific reference to travoprost.

4.2.2 However, the appellants did not clearly identify the embodiment chosen as starting point within D7. They referred to table 1 on page 12 (formulations B1 and B2) as regards the pH, however this passage relates to contact lens disinfecting solutions. This embodiment is not a promising springboard to the claimed ophthalmic travoprost compositions.

4.2.3 The appealed decision selects as starting point formulation B2 on page 16, table 3 of D7, which is a formulation for an undisclosed use comprising
- sorbitol (0.4 w/v%) as a first polyol,
- propylene glycol (1.0 w/v%) as a second polyol;
- 0.6 w/v% sodium borate;
- 0.0002 w/v% polyquaternium;
- further components including tricine, and
having a pH of 7.8.

4.2.4 The subject-matter of claim 1 of the main request differs by:

(i) the use of mannitol;
(ii) the borate concentration of 0.25-0.5 w/v%;
(iii) the amount of polymeric quaternary ammonium compound of 0.0003-0.003 w/v%;
(iv) the presence of travoprost; and
(v) the pH in the range 6.4-7.2.

4.2.5 According to the appealed decision (see §11.3.1.1, page 19), a reduction of the pH value from 7.4 to 6.8 is shown to have a positive effect on the anti-microbial activity against the particular microbial strain *A.Niger*. This effect is indeed supported by a comparison of the antimicrobial activities of examples of the patent differing only by their pH (namely E and Q, or U and T). The appellants did not contest this particular point. Their argument that the (absolute) European Pharmacopoeia A preservation standard is not achieved across the full scope of the claim does not put into question the achievement of this improvement relative to higher pH values as in D7.

4.2.6 But even if the problem is formulated, as proposed by the appellants, as the provision of an alternative composition adapted for treatment of glaucoma, the Board comes to the conclusion that the claimed solution involves an inventive step.

Starting from D7, the skilled person would not arrive at the claimed travoprost compositions in an obvious manner. An essential feature of D7 is the presence of an organic buffer such as tricine, and a pH of the composition normally at or near physiologic pH (i.e. 7.4) (see page 11). Considering additionally that tricine has a useful buffering pH range of 7.4-8.8 (see D33), the skilled person starting from D7 would not have considered adjustments of the pH going beyond the

framework for further development defined by the choice of D7 as starting point, and thus would not have lowered the pH to 6.4-7.2 in the context of an ophthalmic travoprost composition. The skilled person would also not have been incited to do so by the solutions exemplified on page 12 of D7, as they are intended for a different use, namely contact lens disinfection.

4.2.7 Starting from D6

D6 discloses the composition Travatan® Z, which is a travoprost ophthalmic solution comprising 0.25 wt% sorbitol, 0.75 wt% propylene glycol, 1 wt% boric acid, 0.5 wt% HCO-40, and water, and having a pH of 5.7.

The parties agree that the subject-matter of claim 1 of the main request differs by:
(i) the use of mannitol;
(ii) the amount of borate of 0.25-0.5 w/v %;
(iii) the presence of 0.0003-0.003 w/v % polymeric quaternary ammonium compound as antimicrobial preservative; and
(iv) the pH of 6.4-7.2.

The appellants formulate the technical problem as the provision of an alternative BAC-free vehicle for travoprost, and argue that the claimed solution is obvious in light of D7, which would have motivated the skilled person to raise the pH to nearer physiological pH, and hence within the range 6.4-7.2.

However, for the reasons set out above, the Board does not consider that D7 would lead the skilled person to select the claimed pH range of 6.4-7.2 in the context of ophthalmic travoprost formulations.

Accordingly, the main request meets the requirements of inventive step.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division with the order to maintain the patent on the basis of claims 1-10 of the main request filed as auxiliary request 5 with the reply to the appeals of the opponents on 9 June 2020 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated