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Datasheet for the decision of 16 February 2022

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Language of the proceedings: EN

Title of invention:

Aqueous pharmaceutical compositions containing borate-polyol complexes

Patent Proprietor:

NOVARTIS AG

Opponents:

Teva Pharmaceutical Industries Ltd.
Generics (U.K.) Limited

Headword:

Compositions with borate-polyol complexes / NOVARTIS

Relevant legal provisions:

EPC Art. 56
RPBA Art. 12(4)

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
All requests - inventive step (no)

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Case Number: T 0249/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 16 February 2022

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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 28 November 2018 concerning maintenance of the European Patent No. 2722035 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	S. Albrecht
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 722 035 ("the patent") was granted with 21 claims.

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for lack of novelty and lack of inventive step and under Article 100(b) and (c) EPC.

III. The documents filed during the opposition and appeal proceedings include the following:

D1: US 5,505,953
D2: WO 2008/002118 A1
D10: WO 2008/036847 A2
D12: WO 2004/073708
D18: CA 2,088,927 A1
D26: W. Lund, "The Pharmaceutical Codex", 12th edn, London: The Pharmaceutical Press 1994, 312-313
D27: US 6,146,622
D30: R. Voigt, "Lehrbuch der pharmazeutischen Technologie, 6th edn, 1987, pages 368, 416, 421, 422
D31: C. Debbasch et al., Investigative Ophthalmology & Visual Science 43(11), November 2002, 3409-15

IV. The opposition division decided that the patent as amended according to the patent proprietor's main request and the invention to which it related met the requirements of the EPC. In respect of this request, the opposition division concluded, *inter alia*, that the claims of the main request involved an inventive step starting from document D1 or D27 as the closest prior art.

V. Opponent 1 ("appellant I") and opponent 2 ("appellant II") lodged an appeal against the opposition division's decision.

VI. In their statements of grounds of appeal, both appellants requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

VII. In its reply to these statements, the patent proprietor ("respondent") requested that the decision under appeal be set aside and that the patent be maintained as amended on the basis of a set of claims filed as its main request with that reply.

As an auxiliary measure, the respondent requested that the patent be maintained as amended on the basis of one of the sets of claims filed as main request A or auxiliary requests 1, 1A, 2, 2A, 3, 4, 5 and 6, all filed with its reply to the statements of grounds of appeal.

Claim 1 of the main request reads as follows:

"1. A multi-dose ophthalmic composition, comprising:

brinzolamide, brimonidine or a combination thereof as therapeutic agent;

a first polyol, the first polyol being selected from mannitol, sorbitol or a combination thereof, the concentration of the first polyol being at least 0.01 w/v% but no greater than 0.5 w/v%;

a second polyol, the second polyol being selected from propylene glycol, glycerine or a combination thereof,

the concentration of the second polyol being at least 0.1 w/v% but less than 5 w/v% of the composition;

an effective amount of borate, the effective amount being at least 0.05 w/v% and less than 0.5 w/v% of the overall composition;

BAC as an anti-microbial preservative, the concentration of BAC in the composition being greater than 0.00001 w/v% but less than 0.0035 w/v%; and

water,

wherein the composition is a suspension with a therapeutic agent suspended in solution, and wherein the composition comprises an anionic polymer."

VIII. The parties were summoned to oral proceedings. In a communication under Article 15(1) RPBA issued subsequently ("communication"), the board drew the parties' attention to the points to be discussed during the oral proceedings.

IX. By letter dated 17 January 2022, the respondent filed three sets of claims as main request A, auxiliary request 1A and auxiliary request 2A, replacing the previous main request A, auxiliary request 1A and auxiliary request 2A, respectively.

X. Oral proceedings took place on 16 February 2022 in the presence of all parties. The board decided to admit the main request and auxiliary requests 1, 2, 3, 4, 5 and 6 into the proceedings. Document D31, the admittance of which had been contested by the respondent, was also admitted. At the end of the oral proceedings, the Chair announced the board's decision.

XI. The appellants' arguments relevant to the present decision can be summarised as follows.

Admittance of document D31 into the proceedings (appellant II)

Document D31 was *prima facie* highly relevant to all claims on file. It was filed not to prove that BAC did not have a deleterious interaction with anionic polymers, but rather to show that the technical prejudice based on a supposed incompatibility of BAC and anionic polymers reported in section 7.3.5 of the decision under appeal did in fact not exist.

Main request, main request A - claim 1 - inventive step

Both appellants considered document D1 to represent the closest prior art, particularly formulation 10 of example 3.

The subject-matter of claim 1 differed from this formulation on account of:

(a) the presence of brinzolamide, brimonidine or a combination thereof suspended in solution

(b) the presence of an alternative viscosity enhancer, i.e. an anionic polymer, instead of polyvinyl alcohol ("PVA")

(c) the replacement of part of mannitol with a second polyol (propylene glycol, glycerine or a combination thereof at a concentration of at least 0.1 w/v% but less than 5 w/v% of the composition),

such that the mannitol concentration was no greater than 0.5 w/v%

(d) the presence of BAC at a concentration of greater than 0.00001 w/v% but less than 0.0035 w/v%

Appellant I held that the claimed composition did not give rise to any particular technical effect over the closest prior art. Consequently, the objective technical problem was to provide an alternative ophthalmic composition based on a borate-polyol complex which avoided the use of high concentrations of BAC and which had appropriate buffering capacity. Appellant II formulated the objective technical problem as to provide improved preservation efficacy of the ophthalmic formulation constituting the closest prior art by an alternative borate-polyol complex having a low amount of BAC.

Both appellants argued that the solution proposed in claim 1 would have been obvious from the closest prior art in combination with document D10 and the common general knowledge.

In particular, document D1 itself already suggested including a second polyol according to claim 1 (e.g. propylene glycol) in formulation 10 of example 3. In addition, it was well known that propylene glycol could potentiate the antimicrobial effects of other preservatives in pharmaceutical formulations (see document D18, page 14, lines 6 to 10). What is more, the skilled person would have turned to document D10 since it was directed to the same purpose as the patent and document D1. The skilled person would have inferred from document D10 that the lower amount of the first polyol – mannitol or sorbitol – in the compositions of

this document allowed for low resistance to normalisation of tear pH after installation in the patient's eye ("resistance to normalisation of tear pH"), whereas the higher amount of the second polyol – propylene glycol – in these same compositions had a minimal effect on resistance to normalisation of tear pH, as shown in Figures 1 to 3 of this document. These teachings were unrelated to zinc ions and thus applicable not only to borate-polyol systems comprising zinc as the primary preservative but also to other borate-polyol systems, including those disclosed in document D1. In light of these findings, it would have been an obvious course of action to replace part of mannitol with propylene glycol such that the mannitol concentration was no greater than 0.5 w/v%.

As for the claimed concentration of BAC of lower than 0.0035 w/v%, this was merely an arbitrary modification of the 0.004 w/v% BAC used in formulation 10 of example 3 of document D1, which a person skilled in the art would arrive at in a routine manner in view of the teachings of documents D1 and D10 that borate-polyol compositions increased the antimicrobial activity of preservative agents such as BAC.

Concerning the inclusion of brinzolamide and/or brimonidine in the form of a suspension comprising an anionic polymer in formulation 10 of example 3, the opposition division was correct to find that this inclusion was a trivial juxtaposition of features which could not contribute to inventiveness. Specifically, document D12 (see page 7, paragraph 3, and examples 5 to 9) already disclosed the use of brinzolamide and brimonidine for treating glaucoma in the form of a suspension comprising an anionic polymer (Carbopol 974P), mannitol and BAC. Moreover, it was common

practice to formulate ophthalmic compositions comprising poorly soluble therapeutic agents as suspensions containing anionic polymers, as evidenced by document D30 (see section 20.2.3 on page 421, and section 18.4 on page 368).

Contrary to the respondent's view, the disclosures of documents D26 and D27 would not have discouraged the skilled person from adding an anionic polymer as a viscosity enhancer to formulation 10 of example 3 of document D1, despite it containing BAC. Neither of these two disclosures related to borate-polyol buffer systems. What is more, document D1 explicitly suggested that the compositions it disclosed worked with an anionic polymer.

Auxiliary requests 1, 1A, 2, 2A and 3 to 6 - claim 1 - inventive step

In the absence of any surprising technical effect linked to the amendments made to claim 1 of each of these auxiliary requests, the same conclusions in respect of inventive step as for the main request had to be reached.

XII. The respondent's arguments relevant to the present decision can be summarised as follows.

Admittance of document D31 into the proceedings

This document lacked *prima facie* relevance. It did not disclose any antimicrobial studies and therefore could not rebut the common general knowledge, acknowledged by the opposition division in section 7.3.5 of its decision, that BAC interacts with anionic polymers and loses efficacy.

Main request, Main request A - claim 1 - inventive step

Example 5 of document D27 represented the closest prior art. It was directed to the same purpose or effect as the claimed invention and had the most structural features in common. By contrast, document D1 was more remote from the invention on which the patent was based.

If document D1 were nevertheless taken as the closest prior art, in particular formulation 10 of example 3, the objective technical problem to be solved by the claimed invention with regard to this formulation was to be considered that of providing a multi-dose ophthalmic pharmaceutical composition of a different poorly soluble active pharmaceutical ingredient that has a lower resistance to normalisation of tear pH and a lower toxicity and yet still delivers excellent antimicrobial efficacy even in the presence of an anionic polymer. Alternatively, the objective technical problem could be formulated as providing means to improve the comfort and safety profile of formulation 10 of example 3 of document D1 by reducing resistance to normalisation of tear pH and toxicity but without compromising the formulation's antimicrobial activity, even when using a different active pharmaceutical ingredient necessitating the presence of an anionic polymer.

The proposed solution, i.e. a composition in accordance with claim 1, would not have been obvious. First of all, document D1 lacked any pointer towards the claimed therapeutic agent/s. Furthermore, contrary to the appellants' view, the skilled person would not have combined document D10 with document D1 to solve the

stated technical problem. The skilled person would have taken document D10 to be applicable only to compositions comprising zinc as the primary preservative and not to compositions of BAC.

Even if the skilled person had combined document D10 with document D1, the fact remained that neither document D1 nor any other prior art on file would have provided the skilled person with a reasonable expectation of obtaining a multi-dose ophthalmic composition as claimed which had lower toxicity and lower resistance to normalisation of tear pH and yet met the European Pharmacopoeia preservative efficacy standard "A", in spite of:

(a) reducing the BAC concentration by at least 15%,

(b) reducing the mannitol concentration by at least 75% and

(c) introducing an anionic polymer in an amount sufficient to provide suspension of the pharmaceutically active agent,

simply by adding a second polyol within the claimed range.

In fact, the skilled person would have been discouraged from adding an anionic polymer to formulation 10 of example 3 of document D1 in light of the common general knowledge (as evidenced by documents D26 and D27) that BAC bound to anionic polymers, resulting in a loss of antimicrobial effectiveness. This negative effect of anionic polymers on the antimicrobial activity of BAC was further supported by document D2 (see page 7, Table 1, formulation F) and document D27 (see examples 4 and

5) as well as by document D31's disclosure of a corresponding positive effect of Carbopol 974P on BAC toxicity (see page 3414, left-hand column, first full paragraph).

Auxiliary requests 1 and 1A - claim 1 - inventive step

The prior art on file did not provide the skilled person with any incentive to work with combinations of brinzolamide and brimonidine.

Auxiliary requests 2, 2A and 3 to 6 - claim 1 - inventive step

The prior art on file did not contain any pointer that would have prompted the skilled person to lower the effective amount of boric acid from 0.46 wt.% in formulation 10 of example 3 of document D1 to an amount falling within the range recited in claim 1.

XIII. The parties' final requests, in so far as they are relevant to the present decision, were as follows.

Both appellants requested that the decision under appeal be set aside and that the patent be revoked.

Appellant I further requested that:

(a) none of the respondent's claim requests filed with its reply to the statements of grounds of appeal be admitted into the proceedings

(b) the sets of claims filed as main request A, auxiliary request 1A and auxiliary request 2A by letter dated 17 January 2022 not be admitted into the proceedings

The respondent requested that the decision under appeal be set aside and that the patent be maintained as amended on the basis of a set of claims filed as its main request with its reply to the statements of grounds of appeal.

As an auxiliary measure, the respondent requested that the patent be maintained as amended on the basis of one of the sets of claims filed as main request A or auxiliary requests 1, 1A, 2, 2A, 3, 4, 5 and 6, of which:

(a) main request A, auxiliary request 1A and auxiliary request 2A were filed by letter dated 17 January 2022 and

(b) auxiliary requests 1, 2, 3, 4, 5 and 6 were filed with the reply to the statements of grounds of appeal

The respondent further requested that document D31 not be admitted into the proceedings.

Reasons for the Decision

1. The appeals are admissible.

2. Admittance of document D31 into the proceedings (Article 12(4) RPBA 2007)

2.1 Appellant II filed this document with its statement of grounds of appeal.

2.2 Thus, under Article 12(1) RPBA 2020, this document forms part of the basis of the appeal proceedings

unless the board exercises its discretion under Article 12(4), first half-sentence, RPBA 2007 (see Article 25(2) RPBA 2020) not to admit it into the proceedings.

2.3 As outlined in point 1.2 of its communication, the board considers the filing of document D31 to constitute a timely, legitimate reaction to the decision under appeal. As a consequence, the board does not see any reason to exercise its discretion to hold this document inadmissible pursuant to Article 12(4), first half-sentence, RPBA 2007.

2.4 The respondent had argued in writing that document D31 should not be admitted into the proceedings because it was not *prima facie* highly relevant for the discussion of inventive step. In particular, the studies performed in this document did not involve any measurements of antimicrobial efficacy. Therefore, they could not possibly serve as evidence to rebut the established common general knowledge, acknowledged by the opposition division in section 7.3.5 of its decision, that anionic polymers negatively impacted the antimicrobial efficacy of BAC (see reply to the statements of grounds of appeal, paragraph (105)).

2.5 These arguments are not persuasive.

2.5.1 Document D31 is a pre-published scientific paper investigating *in vitro* the cell toxicity and antioxidant effects of two major tear substitutes, i.e. the anionic polymers hyaluronic acid and Carbomer 934P, with and without preservative (see title and abstract, under the heading "Purpose"). The tested cells are conjunctival cells and the preservative used is BAC at concentrations of 0.0005% and 0.005% (see abstract, under the heading "Methods"). The study results are

summarised in the section of the abstract entitled "Results". On the basis of these results, the authors of document D31 conclude, *inter alia*, that the two tested anionic polymers possess antioxidant properties and tend to reduce the toxic effects of BAC in ocular surface epithelial cells (see last paragraph of the abstract).

2.5.2 It is true that document D31 does not refer to any measurements of antimicrobial efficacy. However, appellant II, as explained in its letter dated 14 January 2022 (see page 1), filed this document not to prove that anionic polymers did not negatively impact the antimicrobial efficacy of BAC, but rather to show that the alleged technical prejudice based on a supposed incompatibility of anionic polymers and BAC referred to in the decision under appeal did not exist.

2.5.3 In the board's judgement, document D31 does appear to serve the purpose for which it was filed. As explained in point 2.5.1 above, this document is concerned, *inter alia*, with ophthalmic compositions of anionic polymers preserved with BAC at a concentration of 0.0005%, i.e. a concentration falling within the range recited in claim 1 of the main request. Hence, document D31 discloses subject-matter relevant to the claims of the main request. What is more, this document states that the interaction between BAC and the anionic polymer may in fact be beneficial (see section of the abstract entitled "Conclusions"). This teaching supports appellant II's position that the technical prejudice referred to in the decision under appeal did not exist.

2.5.4 As a result, the respondent's arguments were not able to convince the board.

Main request - claim 1

3. Inventive step (Article 56 EPC)

Object and purpose of the patent

3.1 The patent (see paragraphs [0009] and [0013]) seeks to develop means to enhance the antimicrobial activity of ophthalmic compositions comprising low concentrations of BAC while at the same time ensuring desirable buffering capacity of these compositions.

3.2 To this end, the patent proposes a system composed of two distinct polyols and borate. Specifically, paragraph [0014] states:

"The present invention is directed to a multi-dose ophthalmic composition that includes a first polyol, a second polyol, borate and benzalkonium chloride (BAC). The first polyol is selected from mannitol, sorbitol or a combination thereof. The second polyol is selected from propylene glycol, glycerine or a combination thereof. The borate is included in an effective amount and that effective amount is less than 0.5 w/v% of the overall composition. The BAC is used as an anti-microbial preservative and the concentration of BAC in the composition is greater than 0.00001 w/v% but less than 0.0035 w/v%. The composition is preferably aqueous and is typically at least 70 w/v% and more typically at least 90 or 95 w/v% purified water."

3.3 Contrary to the respondent's contention, the patent is not specifically aimed at achieving good antimicrobial efficacy in suspensions of insoluble drugs.

3.3.1 Notably, the introductory part of the patent (see paragraphs [0001] to [0014]) does not mention drug solubility or refer to ophthalmic compositions comprising insoluble drugs.

3.3.2 The detailed description of the invention on which the patent is based (see paragraphs [0015] to [0058]) does not put any emphasis on the topic of drug solubility either.

3.3.3 Specifically, paragraph [0016] refers to multi-dose ophthalmic compositions in general terms. This disclosure is followed by detailed information on the borate-polyol systems or complexes underpinning the patent (see paragraphs [0018] to [0033]). Paragraphs [0035] to [0037] in turn are dedicated to preservative efficacy standards for multi-dose ophthalmic solutions in different countries, including the European Pharmacopoeia preservative efficacy standards A ("Ph. Eur. A standards") and B ("Ph. Eur. B standards"). Paragraph [0038] teaches the use of the borate-polyol complexes to enhance antimicrobial activity and preservation of various types of ophthalmic compositions, including ophthalmic pharmaceutical compositions, compositions for treating contact lenses (e.g. cleaning products and products for enhancing the ocular comfort of patients wearing contact lenses), ocular lubricating products, artificial tears and astringents.

3.3.4 It is not until paragraph [0039] that the patent discusses the therapeutic agents for use in the ophthalmic compositions in detail. The information that these compositions may take the form of suspensions can be found for the first time in paragraph [0043] of the patent.

The closest prior art

3.4 Both appellants identified document D1, in particular formulation 10 of example 3 ("formulation 10 of document D1"), as the closest prior art for assessing the inventive step of the claimed subject-matter.

3.5 The respondent contested this choice. In its view, document D27 represented the closest prior art.

3.6 A promising starting point is typically a prior art document that relates to the claimed invention, in the sense that it discloses subject-matter conceived for the same purpose or aiming at the same objective, corresponding to a similar use, or relating to the same or a similar technical problem, or at least to the same or a closely related technical field. As a further criterion, the closest prior art should disclose subject-matter having the greatest number of relevant technical features in common with the claimed invention.

3.7 However, this does not mean that another prior art document can be immediately ruled out as a possible starting point merely because it has a different purpose from the invention or fewer technical features in common with the invention than other, seemingly "closer" prior art (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, I.D.3.1). In fact, claimed subject-matter can only be considered inventive under the EPC if it is not obvious starting from any piece of prior art.

3.8 In the case at issue, the board maintains its preliminary opinion set out in its communication that

document D1 can be taken as the closest prior art for assessing the inventive step of claim 1. But even if the board were to agree with the respondent that document D27 should be considered a closer or a more promising starting point, the board would still also need to consider the attack based on document D1. Any other approach would be incompatible with the wording of Article 56 EPC. The invention must involve an inventive step with respect to the whole prior art in order to be eligible for a patent under the EPC.

Distinguishing features vis-à-vis document D1

3.9 It is undisputed that the composition recited in claim 1 differs from formulation 10 of document D1 on account of the following.

(a) The preservative system

(i) The claimed concentration of BAC of greater than 0.00001 w/v% but less than 0.0035 w/v% ("feature (a)(i)") is lower than the concentration of BAC in formulation 10 of document D1 (0.004% by weight).

(ii) The borate-polyol complex of formulation 10 of document D1 comprises mannitol as the sole polyol in a concentration of 2.0% by weight. By contrast, the claimed borate-polyol complex comprises mannitol in a concentration of at least 0.01 w/v% but no greater than 0.5 w/v% of the composition ("feature (a)(ii)") and a further polyol selected from propylene glycol and/or glycerine in a concentration of at least

0.1 w/v% but less than 5 w/v% of the composition ("feature (a)(iii)").

(b) The therapeutic agent is brinzolamide and/or brimonidine ("feature (b)").

(c) The therapeutic agent is suspended in solution ("feature (c)").

(d) The claimed composition comprises an anionic polymer ("feature (d)").

Objective technical problem and solution

3.10 In order to formulate the objective technical problem effectively solved by the claimed subject-matter, the technical effects associated with the distinguishing features need to be identified.

Technical effects linked to features (a)(i) and (a)(ii)

3.10.1 The board accepts that:

(a) Feature (a)(i) (i.e. the claimed concentration range of BAC) provides for an ophthalmic composition having lower ocular toxicity than formulation 10 of document D1.

(b) By virtue of feature (a)(ii) (i.e. the claimed reduced amounts of mannitol), the overall composition recited in claim 1 exhibits a lower resistance to normalisation of tear pH than formulation 10 of document D1 and yet still retains appropriate buffering capacity.

Technical effects linked to feature (a)(iii)

3.10.2 The board is unable to agree with the respondent's contention that feature (a)(iii) (i.e. the presence of the claimed second polyol in the claimed amounts) mitigates the expected loss of antimicrobial activity against *Aspergillus niger* caused by the reduced amounts of the first polyol such that the overall composition recited in claim 1 "meets the 'gold standard' Ph. Eur. A criteria for preservative efficacy".

3.10.3 As acknowledged by the respondent at the oral proceedings, example "I" presented in Table F of the patent is a composition which comprises a preservative system in accordance with claim 1. Yet, this composition does not satisfy the aforementioned "gold standard"; it merely achieves the less strict Ph. Eur. B standards (see Table F, third row, example I, and paragraph [0063]).

Technical effects linked to distinguishing features (b), (c) and (d)

3.10.4 The board agrees with the respondent that these three features taken in combination render the composition recited in claim 1 suitable for treating glaucoma.

The objective technical problem and its solution

3.11 In view of the findings set out in points 3.10.1 to 3.10.4 above, the objective technical problem to be solved by the claimed invention is to provide a further multi-dose ophthalmic composition suitable for treating glaucoma which includes a preservative system causing the composition to have less ocular toxicity and a lower resistance to normalisation of tear pH after

installation in the patient's eye whilst at the same time ensuring that the composition retains appropriate buffering capacity and a level of antimicrobial efficacy sufficient to meet at least the Ph. Eur. B standards.

3.12 The proposed solution to this problem is a composition in accordance with claim 1 comprising, *inter alia*, an anionic polymer. As a consequence, this polymer cannot, contrary to the respondent's view (see section XII.), be included in the objective technical problem (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, I.D.4.2.1).

Assessment of obviousness of the proposed solution

3.13 In the board's judgement, the proposed solution would have been obvious having regard to the state of the art. The reasons are as follows.

3.13.1 The respondent did not dispute that the following was commonly known at the effective date of the patent.

(a) Ophthalmic formulations with lower concentrations of BAC exhibit lower ocular toxicity (see paragraph [0009] of the patent).

(b) Brimonidine and brinzolamide are active agents in the treatment of glaucoma (see document D12, page 2, lines 32 to 34) yet exhibit poor water solubility.

(c) Anionic polymers serve as suspension aids for these agents in aqueous ophthalmic compositions (see document D12, page 7, paragraph 3 and examples 5 to

9, in conjunction with document D30, section 20.2.3 on page 421, and section 18.4 on page 368).

3.13.2 It was equally undisputed that the skilled person would have known that mannitol directly impacts the buffering capacity of borate and therefore the resistance to normalisation of tear pH after application of the composition to the patient's eye (see paragraph [0012] of the patent, and paragraph (31) of the reply to the statements of grounds of appeal).

3.13.3 In particular, Figures 1 and 2 of document D10 show that:

(i) A composition of 0.25 w/v% boric acid alone has practically no buffering capacity over a pH range of 6 to 7.5.

(ii) Adding 0.25 w/v% of mannitol to this composition considerably enhances the buffering capacity of borate and hence the composition's resistance to normalisation of tear pH.

3.13.4 In the light of the above considerations, it would have been straightforward for the skilled person faced with the objective technical problem to make the following modifications to formulation 10 of document D1.

(a) Reduce the concentration of BAC in this formulation so as to fall within the range recited in claim 1.

(b) Replace naphazoline HCl with brimonidine and/or brinzolamide in this formulation.

(c) Select an anionic polymer as a suspension aid for brimonidine and/or brinzolamide instead of PVA.

(d) Lower the concentration of mannitol from 2.0 w/v% to 0.25 w/v% to reduce the formulation's resistance to normalisation of tear pH whilst at the same time ensuring that the formulation retains adequate buffering capacity.

3.13.5 Undeniably, the skilled person would have expected that lowering the concentrations of BAC and mannitol in this manner would negatively affect the overall antimicrobial activity of formulation 10 of document D1. At the same time, the skilled person would have been aware of the fact that:

(a) A different polyol – propylene glycol – has practically no effect on the buffering capacity of borate at concentrations of up to 1.5%, and therefore does not increase resistance to normalisation of tear pH (see Figures 1 and 2 of document D10, and paragraph (69) of the reply to the statements of grounds of appeal).

(b) Complexes of borate and propylene glycol exhibit antimicrobial activity (see document D1, column 1, line 65 to column 2, line 7).

(c) Borate-polyol complexes are used in the compositions of document D1 in an amount between about 0.5 to about 6.0 wt.%, preferably between about 0.5 to 3.0 wt.%, more preferably between about 1.0 to about 2.5 wt.%, and most preferably between about 1.0 to about 2.0 wt.% (see document D1, column 3, lines 3 to 12).

3.13.6 In light of these teachings, the skilled person would have opted for propylene glycol in an amount falling within the range recited in claim 1 to ensure that, despite the aforementioned reduced concentrations of BAC and mannitol, formulation 10 of document D1 retained a level of antimicrobial efficacy sufficient to meet at least the Ph. Eur. B standards. In doing so, the skilled person would have arrived at subject-matter falling within the scope of claim 1 without exercising any inventive skill.

3.13.7 As a consequence, the subject-matter of claim 1 does not involve an inventive step (Article 56 EPC).

Respondent's counter-arguments

3.14 The respondent contended that the skilled person would not have combined document D10 with document D1 to solve the objective technical problem for two reasons. Firstly, document D10 aimed at providing antimicrobially effective compositions which were devoid of conventional antimicrobial preservatives such as BAC. As a solution to this problem, document D10 proposed self-preserved aqueous pharmaceutical compositions comprising zinc and borate-polyol complexes. These complexes were specifically tailored to the unique characteristics of zinc acting as the primary antimicrobial preservative. The skilled person knew from years of prior art that such specific requirements were not needed for BAC. Secondly, the skilled person would have noted that the invention of document D10 was not compatible with anionic excipients, as explained on page 14, lines 11 to 17 of that document.

3.15 Both arguments, however, fail to convince the board.

Document D10 (see page 14, line 33 to page 15, line 7) explicitly states that BAC may, if desired, be present in the zinc-containing compositions, either in conventional amounts or in lower, non-antimicrobially effective concentrations. In light of these teachings, the skilled person would not have considered the compatibility concerns mentioned on page 14, lines 11 to 17 of document D10 to apply to BAC. Hence, the skilled person would not have had any reason to disregard document D10 when confronted with the objective technical problem as defined in point 3.11 above. On the contrary, the skilled person would have studied document D10 in any event to solve the part of the objective technical problem related to reducing the resistance to tear pH normalisation of formulation 10 of document D1. In doing so, the skilled person would have come across the data depicted in Figures 1 and 2 of document D10 and inferred from Figure 2 that, unlike mannitol, propylene glycol does not increase resistance to normalisation of tear pH (see point 3.13.5(a) above).

3.16 In a further line of argument, the respondent submitted that even if the skilled person had turned to document D10 and studied Figures 1 and 2 thereof, they would not have had a reasonable expectation that they could compensate for the significant loss of antimicrobial activity which they would have expected from

(a) lowering the concentration of mannitol of formulation 10 of document D1 by 75%,

(b) lowering the concentration of the primary antimicrobial agent (BAC) by 15% and

(c) adding an anionic polymer to this formulation

by adding a polyol selected from propylene glycol, glycerine or a combination thereof in a concentration falling within the range specified in claim 1.

3.17 The board does not concur. As set out in point 3.13.5(b) above, document D1 already reports on the antimicrobial activity of borate propylene glycol complexes. The board recognises that only borate-mannitol complexes were tested for their antimicrobial activity in the examples of document D1. However, this fact does not lead to the conclusion that the skilled person would have called into question document D1's aforementioned disclosure concerning the antimicrobial activity of borate propylene glycol complexes. Furthermore, as argued by appellant II in writing, it was a known fact at the effective date of the patent that propylene glycol can potentiate the antimicrobial effects of other preservatives (see document D18, page 14, lines 6 to 8). In light of this knowledge, the skilled person would not have expected the loss of antimicrobial activity resulting from replacing part of the mannitol with propylene glycol and slightly reducing the concentration of BAC to be of such an extent that formulation 10 of document D1 would no longer retain a level of antimicrobial efficacy sufficient to meet at least the Ph. Eur. B standards.

3.18 Concerning the addition of an anionic polymer to formulation 10 of document D1, the respondent submitted that document D1 lacked any incentive to use a viscosity enhancer other than PVA. Document D1 (see column 3, lines 13 to 17) merely disclosed carboxyvinyl polymers (i.e. anionic polymers) among a list of qualitatively equal alternative viscosity-enhancing polymers and explicitly stated that PVA was preferred.

In line with this teaching, not a single one of the examples of document D1 pertained to a formulation with a carboxyvinyl polymer. Furthermore, the skilled person would have known from their common general knowledge - as evidenced by documents D26 and D27 - that anionic polymers tended to bind to BAC, resulting in a loss of antimicrobial effectiveness. Further support for this binding could be found in document D31. In view of the foregoing, the skilled person would have been dissuaded from selecting an anionic polymer instead of PVA as a suspension aid in a formulation comprising BAC as the antimicrobial agent (e.g. formulation 10 of document D1).

3.19 The passage of document D1 invoked by the respondent (i.e. column 3, lines 13 to 17) reads as follows.

"The compositions of the present invention useful with RGPs or compositions such as eye drops, gels or ocular inserts will preferably also contain PVA or other viscosity-enhancing polymers, such as cellulosic polymers or carboxy vinyl polymers."

3.20 Hence, contrary to the respondent's view, this passage indicates the same level of preference for PVA, cellulosic polymers and carboxyvinyl polymers, without making any restrictions or limitations in respect of one or more of these three types of polymers.

3.21 The board recognises that none of the formulations illustrated in the examples of document D1 include a carboxyvinyl polymer. However, the teaching of document D1 is not restricted to the examples. It follows that absent any indication or suggestion in the general part of document D1 that carboxyvinyl polymers are less suitable than PVA, the skilled person faced with the

technical problem defined in point 3.11 above would have been motivated to replace PVA in formulation 10 with an anionic polymer.

3.22 This motivation would not have been lessened by the common general knowledge reflected in documents D27 and D26.

3.22.1 Document D27 states in the background section (see column 1, lines 20 to 33) that cationic antimicrobials, such as BAC, tend to bind to the anionic polyelectrolytes (e.g. carboxyvinyl polymers, ion exchange resins) present in ophthalmic formulations, resulting in a loss of antimicrobial effectiveness.

3.22.2 Along the same lines as document D27, document D26 (see page 312, right-hand column, last paragraph) reports that:

"*Benzalkonium chloride and other cationic antimicrobial preservatives are inactivated to varying degrees in the presence of carbomer and other anionic polymers.*"

3.22.3 The board, in agreement with appellant I, understands the term "inactivated to varying degrees" to mean that the degree or extent of inactivation varies depending on the technical setting in question.

3.22.4 The context of document D1 is that of ophthalmic compositions comprising antimicrobially effective borate-polyol complexes. Details of these compositions are provided in the examples. Many of the exemplary compositions comprise a further antimicrobial agent, e.g. BAC. However, D1 is silent about any compatibility issues between BAC and anionic polymers (carboxyvinyl polymers) despite the aforementioned common general

knowledge reflected in documents D27 and D26. By contrast, document D1 (see abstract and column 1, lines 23 to 32) explicitly reports on the incompatibility problems associated with the combination of borate buffers and PVA. In the board's judgement, the skilled person would have concluded from these facts that replacing PVA with an anionic polymer would not negatively affect BAC's antimicrobial activity in the specific context of the formulations disclosed in document D1, and would therefore not have hesitated to replace PVA with a carboxyvinyl polymer in formulation 10 of this document.

3.23 When coming to this conclusion, the board did not overlook the fact that documents D2 (see page 7, Table 1, formulation F) and D27 (see examples 4 and 5) disclose formulations comprising boric acid, one or more polyols and an anionic polymer in the presence of high concentrations of BAC.

3.24 In the respondent's view, it was immediately evident that these elevated BAC concentrations had been chosen to compensate for the loss of antimicrobial activity caused by the interaction of BAC and the anionic polymer.

3.25 The board does not concur. It is undisputed that the concentration of BAC in formulation F in Table 1 of document D2 is rather high (0.022 w/w%). However, the remaining five compositions illustrated in Table 1 likewise comprise an elevated concentration of BAC, yet they contain a non-ionic viscosity-enhancing polymer (hydroxyethyl cellulose) instead of an anionic polymer. As a consequence, the respondent's argument based on formulation F of document D2 must fail.

3.26 The board notes that document D27 (see column 2, lines 58 to 62) relates to topically administrable compositions containing one or more pharmaceutically active agents (e.g. brinzolamide in example 5), an anionic polyelectrolyte, a cationic preservative and one or more of anionic amino acid-based surfactants. The latter are believed to release the bound cationic preservative from the anionic polyelectrolyte by forming a loose and reversible surfactant-preservative complex (see column 2, lines 48 to 52).

3.27 Turning to the examples of document D27, these pertain to compositions comprising BAC at a concentration of at least 0.01%. However, as correctly noted by the appellants, all of these compositions comprise not one but two different anionic polymers. As a consequence, the disclosure of document D27 is not suitable for substantiating the respondent's argument either.

3.28 For the sake of completeness, the board notes that the passage of document D31 relied on by the respondent (see section XII. above, last paragraph of the section entitled "*Main request, Main request A - claim 1 - inventive step*") refers to the binding of anionic polymers to BAC as one of several possible explanations for the observed positive effect of Carbopol 974P on BAC toxicity. However, as submitted by the respondent itself, the studies performed in document D31 did not involve any measurements of antimicrobial efficacy. As a consequence, the aforementioned passage of document D31 is not suitable to support the negative effect of anionic polymers on the antimicrobial activity of BAC reported in documents D27 and D26.

3.29 As a final point, the board notes that the respondent is correct in pointing out that document D1 does not

mention brimonidine or brinzolamide. However, the efficacy of these agents in the treatment of glaucoma was common general knowledge at the effective date of the patent (see point 3.13.1 above). This knowledge forms the technical background for any activities the skilled person performs, feeding into all their decisions. No specific motivation or prompting is required to apply this knowledge (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, I.D.8.3).

3.30 Overall conclusion on inventive step of the main request

In light of the above considerations, the board concludes that the subject-matter of claim 1 lacks inventive step.

Main request A - claim 1

4. Inventive step

4.1 Claim 1 of main request A is identical to claim 1 of the main request.

4.2 Hence, the considerations set out above regarding the inventive step of claim 1 of the main request equally apply to claim 1 of main request A.

Auxiliary requests 1 and 1A - claim 1

5. Inventive step

5.1 Claim 1 is identical in each of auxiliary requests 1 and 1A. It differs from claim 1 of the main request in

that the therapeutic agent is specified as being a combination of brinzolamide and brimonidine.

5.2 As explained in point 3.13.1 above, the efficacy of these agents in the treatment of glaucoma was common general knowledge at the effective date of the patent. As a consequence, it would have been obvious for the skilled person to select combinations of brinzolamide and brimonidine to solve the objective technical problem. No specific motivation or prompting is required to apply this knowledge (see point 3.29 above).

Auxiliary requests 2, 2A and 3 to 5 - claim 1

6. Inventive step

6.1 Claim 1 is identical in each of auxiliary requests 2 and 2A. It differs from claim 1 of auxiliary request 1 (and auxiliary request 1A) in that the upper limit for the effective amount of the borate is reduced to "less than 0.35 w/v%".

6.2 Claim 1 of auxiliary request 3 incorporates the limitations of claim 1 of auxiliary request 2 (and auxiliary request 2A) and further limits the concentration of the first polyol to "at least 0.25 w/v% but less than 0.5 w/v%".

6.3 Claim 1 of auxiliary request 4 incorporates the limitations of claim 1 of auxiliary request 3 and further stipulates that the concentration of the second polyol is at least 0.3 w/v% but less than 1.2 w/v% of the composition.

6.4 Claim 1 of auxiliary request 5 incorporates the limitations of claim 1 of auxiliary request 4 and additionally requires that the effective amount of borate is at least 0.25 w/v% and less than 0.35 w/v% of the overall composition.

6.5 The respondent did not invoke any technical effect/s linked to the aforementioned additional limitations added to claim 1 of auxiliary requests 2, 2A, 3, 4 and 5, beyond those effects asserted for claim 1 of the main request. The objective technical problem is thus the same as for claim 1 of the main request (see point 3.11 above).

6.6 As set out in point 3.13.5(c) above, document D1 suggests using borate-polyol complexes in an amount between about 0.5 to about 6.0 wt.%, preferably between about 0.5 to 3.0 wt.%, more preferably between about 1.0 to about 2.5 wt.%, and most preferably between about 1.0 to about 2.0 wt.%. As a consequence, it would have been a straightforward, routine measure for the skilled person to reduce the amount of borate to the range recited in claim 1 of auxiliary request 5 whilst keeping the level of mannitol below 0.5 w/v% (e.g. at 0.25 w/v%) and selecting amounts of propylene glycol within the range recited in claim 1 of auxiliary request 5, to obtain an overall concentration of the borate-polyol complex of most preferably between about 1.0 to about 2.0 wt.%.

6.7 Consequently, the subject-matter of claim 1 of auxiliary request 5 and that of claim 1 of each of the higher-ranking auxiliary requests 2, 2A, 3 and 4 does not involve an inventive step within the meaning of Article 56 EPC either.

Auxiliary request 6 - claim 1

7. Inventive step

7.1 Claim 1 of auxiliary request 6 incorporates the limitations of claim 1 of auxiliary request 5 and further requires that the lower limit for the concentration of BAC in the composition is "greater than 0.0003 w/v%" (as opposed to 0.00001 w/v% in claim 1 of each of the higher-ranking requests).

7.2 The respondent explained at the oral proceedings that this amendment had been made in the event that the board considered the objective technical problem not to be solved for compositions comprising concentrations of BAC of 0.0003 w/v% or less. No further arguments were submitted by the respondent.

7.3 Nevertheless, the board's reasoning for lack of inventive step of the subject-matter of claim 1 of auxiliary request 5 applies *mutatis mutandis* to the subject-matter of claim 1 of auxiliary request 6, irrespective of whether the objective technical problem has indeed been solved for compositions comprising concentrations of BAC of less than 0.0003 w/v% or not.

7.4 It follows that the subject-matter of claim 1 of auxiliary request 6 does not involve an inventive step within the meaning of Article 56 EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

M. Schalow T. Sommerfeld

Decision electronically authenticated