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Datasheet for the decision of 16 January 2024

Case Number: T 2046/21 - 3.3.07

Application Number: 11745860.4

Publication Number: 2598118

IPC: A61K47/02, A61K47/12, A61K9/08, A61K45/06, A61K9/00

Language of the proceedings: EN

Title of invention:
PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS

Patent Proprietor:
ALLERGAN, INC.

Opponents:
STADA Arzneimittel AG
Bausch Health Ireland Limited
Alfred E. Tiefenbacher (GmbH & Co. KG)
Maiwald GmbH

Headword:
Preservative free bimatoprost / ALLERGAN

Relevant legal provisions:
RPBA 2020 Art. 13(2)
EPC Art. 56

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

Keyword:
Late filed item of evidence - exceptional circumstances (no)
Inventive step - main request and auxiliary requests 1-2 (no)

Decisions cited:
G 0002/21, T 0116/18

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Case Number: T 2046/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 January 2024

Appellant: (Patent Proprietor)	ALLERGAN, INC. 2525 Dupont Drive Irvine, CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
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Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Opponent 2)	Bausch Health Ireland Limited 3013 Lake Drive Citywest Business Campus Dublin D24 PPT3 (IE)
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Respondent: (Opponent 5)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
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Respondent: (Opponent 6)	Maiwald GmbH Elisenhof, Elisenstrasse 3 80335 München (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 September 2021 revoking European patent No. 2598118 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 2 598 118 (hereinafter "the patent") was granted on the basis of 8 claims. The independent claim of the patent as granted read as follows:

"1. A preservative free bimatoprost and timolol composition for use in lowering intraocular pressure in a patient comprising the following formulation: 0.03% w/v bimatoprost; 0.5% timolol; 0.268% w/v sodium phosphate dibasic heptahydrate; 0.014% citric acid monohydrate; 0.68% sodium chloride; water and having a pH of 7.3."

II. Six oppositions were filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. Opponent 4 and opponent 3 withdrew their oppositions on 13 August 2020 and 29 December 2023, respectively.

IV. The opposition division took the decision to revoke the patent. The decision was based on a main request filed on 31 December 2019 and on two auxiliary requests filed on 23 April 2021 and 31 December 2019, respectively.

V. The decision of the opposition division, posted on 14 September 2021, cited *inter alia* the following documents:

D1: Ganfort® Patient Information Leaflet (PIL), Allergan Pharmaceuticals South Africa, 9 October 2009

D4: Baudouin, Acta Ophthalmologica, 2008, 86, pages 716-726,
D7: "EMEA Public Statement on Antimicrobial Preservatives in Ophthalmic preparations for human use", London, 8 December 2009
D9: de Jong *et al.*, Graefe's Arch. Clin. Exp. Ophthalmol., 232, pages 221-224, 1994
D13: Goldberg *et al.*, British Journal of Ophthalmology, 2014, pages 1-6
D16: P. J. Pisella *et al.*, British Journal of Ophthalmology, 2002, 86, 418-423
D24: ANMAT Publication on the eyedrop product Ganfort®
D28: R. A. Lewis *et al.*, J. Glaucoma, 16 (1), 2007, pages 98-103
D29: M. B. Abelson, Review of Ophthalmology, 2009, online article, http://www.revophth.com/content/d/therapeutic_topics/i/1219/c/22958/
D35: Declaration Robinson, 2019
D35a: Leske *et al.*, Ophthalmology, 2007, 114, pages 1965-1972
D35b and D36: Cordeiro *et al.*, Clinical Ophthalmology, 2015, 9, pages 1605-1611
D37: Declaration Chuck Davis, 23.12.2019
D38: Edman, Peter, "Biopharmaceutics of Ocular Drug Delivery" CRC Press, Inc., 1993 , Chap 3, pages 43-59
D39: Mitra, Ashim K., "Ophthalmic Drug Delivery Systems" Marcel Dekker, Inc., 2003, Chap III. 9., pages 281-307
D40: WO 2006/101839 (A2)
D40b: Reply in Opposition proceedings EP 1 753 434 B1 (13 September 2010)
D45: Hamacher *et al.*, Acta Ophthalmologica, 2008, 86:S242, pages 14-19
D46: P. Phillips, "Glaucoma Eyedrops: A Fresh Look at Preservatives", in EyeNet Selections a supplement to Eyenet Magazine, 2008, pages 7-8

D49: FDA Medical Review on Lumigan 0.03%, 2001
D53: Kitazawa *et al.*, 2011, 25, pages 1161 -1169
D54: Hommer, Drugs of today, 2010, 46(6), pages 409-416
D55: Baudouin *et al.*, Progress in Retinal and Eye Research 29 (2010) pages 312-334
D56: Glaucoma Medications and Their Effects on the Corneal Surface. A round table discussion., Supplement to Glaucoma Today, July/August 2007, pages 2-13
D59: Clinical Ocular Pharmacology, Fifth Edition, Chapter 2, Ophthalmic Drug Formulations, 2008, Butterworth-Heinemann (Elsevier Inc.), page 30
D60: Enhancement in Drug Delivery, Chapter 25, pages 527-548, 2007, Taylor & Francis Group, LLC
D62: Bean *et al.*, Survey of Ophtalmology, 2008, vol 53 (suppl 1), pages S69-S84

VI. The opposition division decided in particular as follows:

(a) The main request met the requirements of Articles 123(2) and 83 EPC but the priority date was not validly claimed and the main request did not fulfill the requirements of Article 56 EPC.

(b) Auxiliary requests 1 and 2 likewise contravened Article 56 EPC.

VII. The patent proprietor (appellant) lodged an appeal against the above decision of the opposition division.

VIII. With its statement setting out the grounds of appeal the appellant defended its case on the basis of the main request and auxiliary requests 1 and 2 underlying the appealed decision.

The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 1 of the main request was identical to claim 1 as granted.

Claim 1 of auxiliary request 1 read as follows:

"1. A preservative free bimatoprost and timolol solution for use in lowering intraocular pressure in a patient, comprising the following formulation: 0.03% w/v bimatoprost; 0.68 % w/v timolol maleate; 0.268% w/v sodium phosphate dibasic heptahydrate; 0.014% w/v citric acid monohydrate; 0.68% w/v sodium chloride; water and having a pH of 7.3."

Claim 1 of auxiliary request 2 read as follows:

"1. A preservative free bimatoprost and timolol composition for use in lowering intraocular pressure in a patient, wherein the composition is as follows:

Ingredients	Units	Grade	Amount
Bimatoprost	% w/v	N/A	0.03
Timolol Maleate	% w/v	USP/Ph Eur	0.68
Sodium Phosphate Dibasic Heptahydrate	% w/v	USP	0.268
Citric Acid Monohydrate	% w/v	EUSP/Ph Eur	0.014
Sodium Chloride	% w/v	USP/Ph Eur	0.68
Hydrochloric Acid	% w/v	USP/Ph Eur	pH7.3
Sodium Hydroxide	% w/v	USP/Ph Eur	pH7.3
Purified Water/WFI	Q.S.	USP/Ph Eur	QS

"

IX. The following item of evidence was filed by the appellant on 16 December 2023:

D63: Katz *et al.*, American Journal of Ophthalmology, April 2010, vol. 149, No. 4, pp. 661-671 and 671.e1

X. Oral proceedings were held before the Board on 16 January 2024.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of the auxiliary requests 1 to 2 submitted with the statement setting out the grounds of appeal and corresponding to the requests underlying the appealed decision.

XII. The respondents - opponents 1, 2, 5 and 6 requested that the appeal be dismissed, *i.e.* that the patent be revoked. Respondent - opponent 6 further requested that document D63 not be admitted into the appeal proceedings.

XIII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) Document D63 was to be admitted into the appeal proceedings because it had been filed in direct response to the preliminary opinion of the Board. Moreover it did not introduce any complexity and addressed an issue raised during the proceedings.

(b) The composition of claim 1 of the main request differed from the commercial product Ganfort® as disclosed in document D1, which represented the closest prior art composition, in that it did not contain benzalkonium chloride (BAK). The removal of BAK resulted in an improvement of the intraocular pressure (IOP) lowering. This effect demonstrated in the post-published documents D13, D35, D36 and D37 was to be taken into account according to G 2/21. The objective technical problem resided

consequently in the provision of an improved composition for lowering IOP achieving greater IOP reduction. None of the prior art documents suggested that the removal of BAK from the commercial product Ganfort® would result in an improved efficacy in lowering IOP. Furthermore even if the problem to be solved was formulated as the provision of a composition for lowering IOP with maintained efficacy, the solution offered in claim 1 of the main request was still not obvious over the cited prior art. BAK was generally known to be a penetration enhancer in addition to a preservative. Furthermore, the skilled person would have been aware from documents D40 and D40b that BAK improved the permeability and IOP lowering efficacy of bimatoprost. These documents outweighed the other cited documents since they concerned the launch of the commercial product Lumigan 0,01 which happened around one year before the priority date. Finally as stated during oral proceedings bimatoprost was known to be the most active agent in the composition and there was no interaction between bimatoprost and timolol. It followed that the skilled person would not have had any reasonable expectation of success of maintaining IOP lowering efficacy when removing BAK from Ganfort®. Hence, the main request met the requirements of Article 56 EPC.

(c) Auxiliary requests 1 and 2 also met the requirements of Article 56 EPC.

XIV. The arguments of the respondents - opponents 1, 2, 5 and 6, as far as relevant for the present decision, can be summarised as follows:

(a) Respondent - opponent 6 considered that document D63 should not be admitted into the appeal proceedings because it should have been filed earlier. Respondent - opponent 2 underlined that the issue addressed by document D63 had already been discussed during the first instance proceedings.

(b) The composition of claim 1 of the main request differed from the commercial product Ganfort® as disclosed in document D1, which represented the closest prior art composition, in that it did not contain benzalkonium chloride (BAK). Respondents - opponents 2, 5 and 6 contested that the effect allegedly demonstrated in the post-published documents D13, D35, D36 and D37 was to be taken into account according to G 2/21. Furthermore according to all respondents, documents D13, D35 and D37 did not appropriately substantiate any improvement of the IOP lowering of the claimed composition compared to Ganfort®. Accordingly the objective technical problem could be formulated as in the impugned decision, namely as the provision of an alternative combination treatment for lowering IOP comprising bimatoprost and timolol with maintained efficacy while being safe and tolerable. At the priority date of the patent a trend for preservative free ophthalmic compositions existed (see *e.g.* D4, D7 and D54). There were furthermore many documents in the prior art disclosing that BAK had no influence on the IOP lowering activity of prostaglandin analogues (see *e.g.* D59, D29, D55, D56, D57 and D46). Besides D49 showed that BAK had no effect on the IOP lowering efficacy of bimatoprost. The references cited by the appellant (D38, D39, D40) were either outdated

and/or provided merely *in vitro* permeability or animal data. As a result, the skilled person would have had a reasonable expectation of success of maintaining IOP lowering efficacy when removing BAK from Ganfort®. Hence, the main request did not meet the requirements of Article 56 EPC.

(c) Auxiliary requests 1 and 2 did not meet the requirements of Article 56 EPC for the same reasons as detailed for the main request.

Reasons for the Decision

1. Admittance of the new item of evidence D63

1.1 Document D63 was filed by the appellant with its submission of 16 December 2023, *i.e.* after notification of the summons to oral proceedings and of the communication pursuant to Article 15(1) RPBA. The issue of its admittance into the appeal proceedings is to be determined in accordance with Articles 13(1) and 13(2) RPBA.

1.2 According to the appellant, this document was filed in response to the detailed preliminary opinion of the Board, in particular the finding that document D40 provided only permeation data and no data on intraocular pressure (IOP) lowering effects. Document D63 would back up the data regarding penetration of document D40 by substantiating that also the IOP lowering effect was improved. The submission of document D63 would merely be that of a factual evidence to support a factual point. Furthermore it would not introduce any complexity and would address a controversial point raised during the proceedings.

1.3 According to Article 13(2) RPBA, a document filed at this stage of the appeal proceedings is, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

In the present case, the appellant has not provided any exceptional circumstances justified by cogent reasons for the submission of document D63 at this late stage of the appeal proceedings.

In particular, as stated by the respondents - opponents 2 and 6 during the oral proceedings, the issue of penetration enhancement not being directly correlated to an increased reduction of IOP had already been raised by the respondents during the appeal proceedings (see *e.g.* reply to the statement of the grounds of appeal of respondent - opponent 2, item 98). This issue was thus not newly raised in the preliminary opinion of the Board, which cannot thus constitute an exceptional circumstance. Hence, document D63 should have been filed earlier in support of document D40 in response to the respondents submissions.

1.4 The Board therefore does not admit this document in the appeal proceedings (Article 13(2) RPBA).

Main request

2. Inventive step

2.1 Closest prior art and distinguishing feature

2.1.1 The patent relates to preservative-free formulations of bimatoprost and timolol for use in reducing IOP, in particular in the treatment of glaucoma. The main

purpose of providing a preservative-free formulation is to avoid the unwanted side-effects associated with preservatives, in particular benzalkonium chloride (BAK), while at least maintaining the efficacy in terms of IOP lowering (see paragraphs [0007] and [0011]).

2.1.2 In line with the impugned decision, all the parties considered the commercial product Ganfort® as disclosed in document D1 to represent a valid choice as closest prior art document. The Board sees no reason to differ.

2.1.3 Document D1 discloses the commercial product Ganfort®, which is an eye drop formulation containing 0.03% w/v bimatoprost and 0.5% w/v timolol as active ingredients as well as benzalkonium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate and sodium chloride as excipients and water. It was undisputed amongst the parties that the amounts of excipients (with the exception of the preservative benzalkonium chloride) and the pH of the composition of Ganfort® are the same as presently claimed. This was confirmed by document D24.

2.1.4 It was furthermore common ground that the composition of claim 1 of the main request differed from the commercial product in that it was preservative-free while Ganfort® contained BAK.

2.2 Technical effects

2.2.1 It was undisputed that the removal of BAK from the composition resulted in the avoidance of unwanted effects directly linked to BAK. This would allow the composition to be used by patients hypersensitive to BAK and patients wearing soft contact lenses (see patent, paragraph [0007]).

2.2.2 The parties however disagreed with regard to the effect on the IOP lowering linked to the removal of BAK from the closest prior art composition.

Consideration of post-published evidences

2.2.3 The patent only provided an example of the claimed composition (see table 1) and did not provide any experimental data regarding its use in reducing IOP. The appellant relied on post-published evidence (D13, D35, D36, D37) to substantiate an improved/maintained efficacy for the BAK-free composition compared to a composition containing BAK. Respondents - opponents 2, 5 and 6 contested in the written and/or oral proceedings the possibility of relying on post-published data to backup said effect in line with G 2/21 and its interpretation provided in T 116/18.

2.2.4 According to G 2/21, "a patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention" (see Order 2.).

2.2.5 In the present case, the Board considers that an IOP lowering effect of the claimed combination would have been expected at the filing date. It was indeed common general knowledge at the filing date of the patent, that both active ingredients of the claimed formulation, bimatoprost and timolol, were used to reduced IOP. This was not disputed by an party. Also the combination of both agents had already been used in the commercial product Ganfort® for lowering IOP.

Furthermore, the maintenance/improvement of the IOP lowering effect compared to a preserved composition was generally described in the original application on page 2 lines 6 to 10 and page 4 lines 8 to 13 (corresponding to paragraphs [0007] and [0011] of the patent).

Accordingly, the Board considers that the alleged effect relied upon by the appellant was derivable from the original application. The technical effect regarding IOP lowering was thus encompassed by the technical teaching of the original application as required by G 2/21.

2.2.6 Furthermore, this technical teaching applied to the presently claimed combination, since it was specifically claimed and exemplified in the original application. This effect did thus not change the nature of the claimed invention, *i.e.* the claimed composition, as defined in G 2/21 (see last sentence of paragraph 93), so that it was embodied by the same originally disclosed invention in the sense of G 2/21.

2.2.7 In line with G 2/21, the alleged technical effect on improvement/maintenance of IOP lowering in so far as it is supported by the post-published experimental data provided in documents D13, D35 and D37 is thus to be taken into account when assessing the inventiveness of the claimed subject-matter.

2.2.8 In this context, respondents - opponents 2 and 6 contested during oral proceedings that the alleged effect of maintained/improved efficacy would be embodied by the original application as foreseen by G 2/21 in light of its interpretation as provided in T 116/18 (see paragraph 11.14). There would indeed be

legitimate reasons to doubt that an improved or maintained efficacy could be achieved due to the removal of the preservative BAK.

Independently of the relevance of the interpretation provided in T 116/18 for the present case, this argument is not convincing. No consensus existed in the cited prior art at the filing date on the potential effect of BAK as penetration enhancer for the claimed active ingredients, let alone an effect on improving the efficacy of the composition in lowering IOP (see D9, D29, D38, D39, D40, D49, D59, D60). There was therefore no legitimate reason to doubt a priori that the effect mentioned in the application as originally filed could be achieved.

2.2.9 The appellant also referred to document D36, a post-hoc analysis of the data of document D13. It compares the improvement of IOP lowering in presence and absence of BAK in two different patient groups, treatment naive patients *versus* pre-treated patients. The conclusion of the article is that there is an improvement in IOP lowering effect in treatment naive patients *versus* pre-treated ones in case of preservative-free Ganfort (Ganfort PF) but no such difference with Ganfort®.

Neither the original application nor the patent mentioned or even suggested this very specific effect regarding IOP lowering in a particular sub-group of patients. There was nowhere any distinction between treatment naive and pre-treated patients.

The argument of the appellant that the effect highlighted in document D36 would not be a new one but merely the same as in document D13, which would simply be observed in a magnified manner in the subgroup of

treatment naive patients, is not convincing. Document D36 does indeed refer to an effect observed in a particular subgroup of patients compared to the remaining patients. The fact that it would reside in a further improvement of an effect allegedly already occurring in the remaining patients does not change the fact that the effect supported by document D36 applies only to a subgroup of patients not previously identified or suggested in the patent.

Consequently no such effect on a specific subgroup of patients was encompassed nor embodied by the technical teaching of the originally disclosed subject-matter. Hence, according to G 2/21, this specific technical effect (*i.e.* improvement of IOP reduction in treatment naive patients) cannot be relied upon for the assessment of inventive step.

Alleged improvement of IOP lowering

2.2.10 The appellant brought forward that the preservative free compositions of the invention would provide an improved IOP lowering compared to compositions containing BAK, as shown by documents D13, D35 and D37. This alleged improvement of IOP lowering effect was disputed by all the respondents. In particular, the parties disagreed on the statistical relevance of the results of documents D13 and D37 and the significance of the confidence interval.

2.2.11 In document D13 a comparison of the efficacy in IOP lowering of preservative-free Ganfort (Ganfort PF) and Ganfort® is provided (see figures 2-3). Two data sets (worse eye IOP in *per protocol* (PP) group, figure 2, and average eye IOP in intention-to-treat (ITT) group, figure 3) provide the difference between the IOP

lowering obtained with Ganfort PF (difference versus baseline IOP) and the one obtained with Ganfort® (difference versus baseline IOP). Negative results would indicate a superior reduction of IOP with Ganfort PF compared to Ganfort®. In case of a "0" value for the difference, both compositions would be equivalent in terms of efficacy.

While, as argued by the appellant, some numerical values are negative, it remains that in both cases the value of "0" is encompassed by the 95% confidence intervals. This led the authors of document D13 to conclude to an equivalent efficacy in IOP lowering.

2.2.12 In document D37, which consists in a statistical analysis of some data of document D13, confidence intervals of 72.1% (for the worse eye in PP group) and 73.8% (for the average eye in ITT group) were calculated based on the data of document D13 at 12 weeks. The appellant explained that the data at week 12 were used because they are the most relevant for a long-term treatment. The author of document D37 concludes that conducting an analysis using the average of the three values obtained at week 12 confirms the improvement of IOP lowering in the absence of BAK with these confidence intervals. The Board observes that the choice of confidence intervals of around 70% is not supported by any other document cited in the procedure.

2.2.13 Document D35 is an expert declaration and does not provide additional experimental data. The Board notes that, as mentioned by the respondents, this declaration remains an isolated opinion.

2.2.14 The Board observes that the appellant chose to cite document D13 in support of an alleged technical effect.

However the arguments of the appellant concentrated on the results provided in Figures 2 and 3, with a significant effort of interpretation thereof as revealed by documents D35 and D37. It remains nevertheless that, when considering the disclosure of document D13 as a whole, there is no unambiguous teaching of a generally improved efficacy in the treatment of IOP for Ganfort PF compared to Ganfort®. As detailed above (see 2.2.11), the experimental data do not unambiguously support a systematic occurrence of such an effect and the authors of document D13 conclude to the mere equivalence of both compositions.

In this context the appellant referred to an isolated statement in document D13 under the section "Discussion" on page 5 left column 1st full paragraph mentioning that "differences between the treatments in IOP lowering consistently favouring bimatoprost/timolol PF". This passage however follows the statement that "The principal conclusion is that bimatoprost/timolol PF demonstrated non-inferiority and equivalence in IOP lowering compared with bimatoprost/timolol". The passage mentioned by the appellant appears to refer to the isolated values of figures 2 and 3 without taking into account any confidence interval at all. The Board considers that this statement, when taken together with the entire sentence to which it belongs, does not change the overall teaching of document D13, which is summarised in the first sentence of the last paragraph as follows "In conclusion, bimatoprost/timolol PF provided an effective IOP-lowering **alternative** to bimatoprost/timolol for patients who are not sufficiently controlled on monotherapy and/or are sensitive to preservatives" (emphasis added).

2.2.15 Furthermore, the argument of the appellant that the study of document D13 was designed as a "non-inferiority" and "equivalence" study thus explaining that the conclusion of the authors did not pertain to any superiority is also not convincing. This argument appears to be of speculative nature and it would be wrong to read more out of a document than what is clearly derivable therefrom.

2.2.16 Moreover, even if the Board may concur with the appellant's argument that different levels of proof were required for regulatory purposes and for patent law purposes, the Board still considers that an item of evidence cited in support of a technical effect should not be reinterpreted in a way that goes beyond its actual teaching. In the Board's view, the calculations provided in document D37 and the explanations contained in document D35 cannot overturn the overall clear teaching of document D13 which is merely that the IOP lowering effect is maintained in Ganfort PF compared to Ganfort®.

2.2.17 Accordingly there is no unambiguous experimental data on file which would allow to conclude to a significant improvement of IOP lowering for Ganfort PF compared to Ganfort®. It remains nevertheless that the experimental data provided in document D13 support the fact that IOP lowering efficacy is maintained when using Ganfort PF compared to Ganfort®.

2.3 Objective technical problem

The objective technical problem can thus only be formulated as the provision of an alternative combination treatment for lowering IOP which maintains efficacy while being safe and tolerable.

2.4 Obviousness of the solution

2.4.1 It was undisputed that the adverse effects of BAK formed part of common general knowledge at the filing date as well as the general recommendation of removing preservatives such as BAK from eye drop formulations when said adverse effects were to be avoided (see *e.g.* D4, page 723, 3rd column, 1st full paragraph; D7, 1st bullet point; D16, abstract "conclusions"; D46, page 7 middle column, 3rd full paragraph and paragraph bridging middle and right columns; D54, "summary"; D55 page 331, paragraph bridging both columns; D59, page 30).

2.4.2 The main point of dispute was whether the skilled person would have had a reasonable expectation of success in maintaining the IOP lowering efficacy when removing BAK from Ganfort®.

2.4.3 The parties referred to a great number of prior art documents to determine the common general knowledge of the skilled person regarding BAK and its role as penetration enhancer and possibly activity enhancer at the priority date.

2.4.4 It appears that BAK was initially commonly recognised as enhancing penetration of drugs into the eye anterior chamber through disruption of the hydrophobic barrier of the corneal epithelium (see *e.g.* D55, page 315, 2nd paragraph but also D59, page 30, D60 page 537 section 25.4.3 and D38, page 46, 2nd full paragraph). However, later studies questioned this role for some drugs, in particular prostaglandin analogs which are lipophilic compounds and for which a penetration enhancer is less important (see *e.g.* D55, page 315, paragraph bridging

both columns; D56, page 5 left-hand column, 3rd paragraph; D46, page 7, left column, 2nd paragraph).

Independently of the disputed issue of whether bimatoprost could be considered as a prostaglandin or not, it remains that it is a lipophilic drug and that, on the basis of the cited prior art, no consensus on the role of BAK on the permeability of lipophilic drugs appeared to exist at the priority date.

2.4.5 Moreover, several studies showing that BAK-free prostaglandin analogs formulations were equivalent in terms of IOP lowering to BAK preserved formulations were cited (see *e.g.* D4, page 723, 2nd column, last paragraph; D54, "Conclusion"; D46, page 8, middle column; D31, abstract; D53, abstract and page 1167, left column, 2nd full paragraph; D29, page 4, 3rd paragraph; D62, abstract; D28, abstract; D45, abstract).

2.4.6 In so far as the active agents of the present composition are concerned, the cited documents provided the following information:

- for timolol: document D9 (see page 224 last paragraph) substantiated that a BAK free timolol formulation was as effective in reducing IOP as a BAK preserved timolol formulation while document D39 (see page 291, table 4) stated that ocular absorption of timolol was enhanced in presence of 0,025% BAK, and

- for bimatoprost: documents D40, D40b and D49 provided different results.

Document D40 (see examples 2 and 4) substantiated an improvement of the permeability of bimatoprost in presence of BAK, but did not provide evidence concerning IOP reduction.

Document D40b (see figure on page 6) reported the results of a study on compositions containing 0,01% or 0,0125% bimatoprost and 200 ppm benzalkonium compared to Lumigan (containing 0.03% bimatoprost and 50 ppm BAK). All compositions achieved similar IOP reduction, which led the appellant conclude that BAK would improve the activity of bimatoprost since the same level of activity was obtained with 3 times less bimatoprost but 4 times more BAK. The Board however notes that this constitutes an indirect conclusion reached without any negative control (*i.e.* composition without any BAK).

On the other hand document D49 showed that a BAK preserved bimatoprost formulation had a similar IOP lowering effect as a BAK free bimatoprost formulation (see pages 105/124 to 111/124). In this context, the argument of the appellant that no BAK free formulation was launched following the results of document D49 does not undermine the teaching of this document, especially as many different considerations play a role in commercialisation of pharmaceutical products.

The Board cannot share the view of any of the parties on the fact that one or more of these documents, *i.e.* one or more of the studies those results are reported in the documents, should be given more weight than another. The skilled person working in the field of ophthalmic compositions for use in reducing IOP would

have been aware of all the cited documents and would have considered them equally.

In particular, the fact that Lumigan 0,01 was launched to replace Lumigan 0,03 would not give more weight to the findings in documents D40 and D40b than D49, contrary to the opinion of the appellant.

Finally, the argument of the appellant provided during oral proceedings that the results in document D49 cannot be correct was not substantiated by further evidence. The mere fact that some other isolated results were considered by the appellant not to make sense (comparison of preservative free compositions with 0,06% and 0,03% active agent and some isolated adverse effect decreasing with increased amount of bimatoprost) does not mean that all the results provided in this document are not correct.

2.4.7 Hence, in view of the entirety of the items of evidence, it cannot be concluded that there was any consensus on the role of BAK on IOP lowering in compositions comprising bimatoprost or timolol. Contrary to the opinion of the appellant, there was in particular no unambiguous teaching that BAK would enhance the IOP lowering efficacy of any of these drugs, while it was shown to have no incidence on the efficacy of many other IOP lowering lipophilic drugs.

As a consequence, the skilled person would not have had legitimate reasons to expect a loss of efficacy when removing BAK from Ganfort®. On the contrary, the Board is of the opinion that the skilled person would have had a reasonable expectation of success in maintaining IOP lowering efficacy of Ganfort® when removing BAK

from the formulation to avoid the adverse effects linked to this preservative.

2.5 Accordingly, the main request does not comply with the requirement of inventive step (Article 56 EPC).

Auxiliary requests

3. Inventive step

3.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that (i) the composition was specified as being a solution and (ii) the timolol component was specified as timolol acetate.

3.2 Claim 1 of auxiliary request 2 has been limited to a specific composition by including the list of all components and their respective amounts.

3.3 The further features specified in auxiliary requests 1 and 2 are already part of Ganfort® as revealed by documents D1 and D24. In any case they have not been shown to be linked to any particular technical effect. This was not disputed by the appellant.

3.4 Hence, the reasoning regarding the lack of inventive step developed for the main request applies *mutatis mutandis* to auxiliary requests 1 and 2.

3.5 As a result, auxiliary requests 1 and 2 do not meet the requirement of inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated