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Datasheet for the decision of 13 June 2017

Case Number: T 1682/15 - 3.3.01

Application Number: 03726234.2

Publication Number: 1496912

IPC: A61K31/535, A61K31/498, A61P27/06

Language of the proceedings: EN

Title of invention:
COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE

Patent Proprietor:
ALLERGAN, INC.

Opponents:
STADA Arzneimittel AG
Alfred E. Tiefenbacher (GmbH & Co. KG)
Teva Pharmaceutical Industries LTD.
Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi
Hexal AG
Generics [UK] Limited

Headword:
Combination of brimonidine and timolol/ALLERGAN

Relevant legal provisions:
EPC Art. 54, 55(1)(a), 56
RPBA Art. 13(1), 13(3)

Keyword:
Late-filed submission in relation to Article 55 EPC - admitted (no)
Late-filed auxiliary requests - admitted (yes)
Novelty - (yes)
Inventive step (all requests) - (no)

Decisions cited:
G 0003/98, T 1064/08, T 0167/93

Catchword:

Europäisches Patentamt
European Patent Office
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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1682/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 June 2017

Appellant: (Patent Proprietor)	ALLERGAN, INC. 2525 Dupont Drive Irvine, CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent 01: (Opponent 1)	STADA Arzneimittel AG Stadastrasse 2-11 61118 Bad Vilbel (DE)
Representative:	Hamm & Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent 02: (Opponent 2)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Feldmann, Ute Patentanwaltskanzlei Feldmann Leipziger Platz 15 10117 Berlin (DE)
Respondent 03: (Opponent 3)	Teva Pharmaceutical Industries LTD. 5 Basel Street Petah Tiqva 49131 (IL)
Representative:	Best, Michael Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstrasse 2 80538 München (DE)

Respondent 04: (Opponent 4)	Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi Hosdere Mevki Tunc Caddesi, No. 3 34555 Hadimkoy, Istanbul (TR)
Respondent 05: (Opponent 5)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Hinterberg, Katherine Sandoz International GmbH Industriestraße 25 83607 Holzkirchen (DE)
Respondent 06 : (Opponent 6)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 July 2015 revoking European patent No. 1496912 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 496 912 is based on European patent application No. 03726234.2, filed as an international application published as WO2003/088973.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(3) Larsson, Arch ophthalmol, April 2001, 492-495

(4) Yüksel et al., Ophthalmologica, 1999, 228-233

(6) Rote Liste 2001, entries 67001-67003, 67130-67147, 67154-6767193 and 67194-67201

(8) Final Study Report: "A Comparison of the Safety and Efficacy of Twice—Daily vs. Three-Times-Daily Administration of Brimonidine 0.2 %, in Subjects with Open-Angle Glaucoma or Ocular Hypertension", Allergan Study Number A342-119-7831

(9) Derick, Ophthalmol, 1138—54

(19) DE-A1-4201079

(20) Noecker, Advances in Therapy 2001, 205-215

(21) Arici, Eye 2002, 39-43

(28) Stamper, Survey of Ophthalmology, 2002, 63-67

(30) Goni, European Journal of Ophthalmology, 2005, 581-590

(31) Sall et al., Abstract Issue, Annual Meeting Fort Lauderdale Florida, April 29-May 4, 2001 in IOVS, Abstract 4412-B431

(32) Fechtner et al.: "The Future of Glaucoma Diagnosis and Therapy", Chapter 25 in Primary Care of the Glaucomas, 2000

(37) British National Formulary, 2002, 510-514

(42) Submission Patentee 19 August 2011

(50) Alphagan® P 0.15 % product label text

(51) Alphagan® P 0.1 % product label text

(53) U.S: Department of Health and Human Services, Statistical Review and Evaluation, NDA # 21,398

(56) Rote Liste 1993: Timolol

(60) Center for Drug Evaluation and Research, Medical Reviews Application No. 21-398

(61) Clinical Review, W.M.Boyd, NDA 21-398, Combigan, chapters 3-9

(62) Clinical Study Report: "A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2 % Brimonidine Tartrate/0.5 % Timolol Fixed Combination Ophthalmic Solution Compared with ALPHAGAN® (0.2 % Brimonidine Tartrate) TID (Three Times Daily) and 0.5 % Timolol BID Given Concurrently in Glaucoma or Ocular Hypertension Patients for Ten Days", Study Number 190342-024T

(64) Motolko, Current Med. Res., 2008, Vol. 24, 2663-2667

(65) Collection of documents concerning the professional relationship of Dr Stamper with Allergan

(66) Declaration of Dr Davis dated 3 December 2015

(69) Study report on 024T, pages 38, 42, 72-76

III. The present appeal lies from the decision of the opposition division to revoke the patent under Article 101(3)(b) EPC.

The opposition division held that the subject-matter of the claims of all requests lacked, *inter alia*, inventive step when starting from either document (28) or any of documents (3), (4), (21) and (31).

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

V. In a communication pursuant to Article 15(1) RPBA dated 10 February 2017, the board informed the parties of its preliminary opinion on some of the issues at stake. Oral proceedings were held before the board on 12 and 13 June 2017 in the absence of respondent 4.

VI. Three sets of claims, the main request and auxiliary requests 4A and 10A, form the basis for the present decision.

The independent claims 1 of these requests read as follows:

Main request:

"1. An ophthalmic pharmaceutical composition for use in a method of treatment of glaucoma or ocular hypertension, the composition comprising an effective amount of brimonidine tartrate and an effective amount of timolol maleate in a pharmaceutically acceptable carrier therefor."

Auxiliary request 4A:

"1. An ophthalmic pharmaceutical composition for topical use in a method of treatment of glaucoma, the composition comprising an effective amount of brimonidine tartrate and an effective amount of timolol maleate in a pharmaceutically acceptable carrier therefor, wherein the concentration of brimonidine tartrate is 0.2 %(w/v) and the concentration of the timolol maleate is 0.68 %(w/v)."

Auxiliary request 10A:

"1. An ophthalmic pharmaceutical composition for topical use in a method of treatment of glaucoma, the composition comprising an effective amount of brimonidine tartrate and an effective amount of timolol maleate in a pharmaceutically acceptable carrier therefor, the composition being for twice-daily administration, wherein said composition consists of:

Ingredient	**Function**	**Concentration, %(w/v)**
Brimonidine Tartrate	Active	0.2
Timolol Maleate, EP	Active	0.68[1]
Benzalkonium Chloride, NF, EP	Preservative	0.005

Sodium Phosphate, monobasic monohydrate, USP	Buffer	0.43
Sodium Phosphate, dibasic heptahydrate, USP	Buffer	2.15
Sodium Hydroxide, NF	pH adjust	Adjust pH to 6.9
Hydrochloric Acid, NF	pH adjust	Adjust pH to 6.9
Purified Water, USP, EP	Solvent	q.s. ad

[1]Equivalent to 0.5 %(w/v) Timolol, free base"

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Submissions relating to Article 55(1)(a) EPC

The disclosure of document (28) was not to be taken into consideration as prior art under Article 54(2) EPC since it had occurred as a consequence of an evident abuse in relation to the appellant within the meaning of Article 55(1)(a) EPC. Dr Stamper, the author of document (28) and one of the appellant's consultants, had disclosed information in document (28) in breach of his obligation of confidentiality. Document (28) was published within six months of the priority date of the patent in suit. Contrary to the interpretation of the Enlarged Board of Appeal, it was the priority date which was relevant in the context of Article 55 EPC.

The appellant found itself in a special situation since its argumentation in relation to Article 55 EPC and its applicability to document (28) was directly related to its request for re-referral to the Enlarged Board with a view to setting aside G 3/98. Because the opposition division could not make a referral there had been no point in raising the issue of document (28) and Article 55 EPC in the opposition proceedings. The issue had been raised at the earliest possible point in time,

namely with the statement setting out the grounds of appeal. The appellant had no correspondence with Dr Stamper from which it was derivable that he had asked for permission to publish document (28). Document (65) clearly showed that Dr Stamper, when publishing document (28), had breached his obligations set out in the confidentiality agreement. The facts were thus clear cut. The respondents had not shown that the information about the combination of timolol and brimonidine presented in document (28) could be found anywhere in the public domain. Also, as was apparent from their letters of reply, all the respondents had had an opportunity to react to the submissions.

Admission of auxiliary requests 4A and 10A

Auxiliary requests 4A and 10A had been filed quickly in response to the board's communication pursuant to Article 15(1) RPBA. These requests addressed the issues under Article 123(2) EPC and contained only minor amendments as compared with the corresponding former requests that had been filed together with the statement of grounds of appeal. The changes did not make the case more complex and were intended to streamline the proceedings.

Main request

The main request was novel over document (28), since neither the specific salts of timolol and brimonidine nor the safe and effective treatment of glaucoma with the fixed combination were disclosed therein.

Starting from the disclosure of any of documents (3), (4), (21) and (31) the difference in subject-matter of claim 1 of the main request lay in the fixing of the

combination of brimonidine tartrate and timolol maleate. The logical combination of the outcomes of the studies 190342-024T - the "024T study" (see documents (42), (53), (60), (62) and (69)) - and A342-119-7831 - the "7831 study" (document (8)) - established evidence for the technical effect of reduced somnolence due to the fixing of the combination of brimonidine tartrate and timolol maleate. The study 024T clearly showed a highly significant effect on sleepiness for a large patient group. Due to the set-up of this study, the effect could only be due to either the fixing of the combination or the change from TID to BID administration for brimonidine tartrate. The 7831 study proved that there was no difference in sleepiness/ somnolence/fatigue (which were considered equivalents by the patients) between TID and BID administration of brimonidine tartrate. The only possible conclusion was thus that the effect shown in the 024T study was due to the fixing of the combination. The "507T study" (see document (30)) could not be taken into consideration, since it had a different washout regimen at the beginning of the study and, most importantly, collected data on side effects only by open questions. Thus, on the balance of probabilities, which was the correct legal standard to apply, the effect of reduced somnolence was linked to the fixing of the combination. This conclusion had also been reached in decision T 1064/08 and was further reinforced by the expert declaration in document (66). Patient compliance was always an issue in therapy, but was of lesser importance than the reduction of a serious side effect. The technical problem was the provision of a formulation for treating glaucoma that had good efficacy, improved safety and compliance and a reduction of the side-effect somnolence. No other document suggested the fixing of the combination of

brimonidine tartrate and timolol maleate as the solution. There was thus an inventive step.

Auxiliary request 4A

Claim 1 of auxiliary request 4A specified the concentrations of the active ingredients. Of special importance was the concentration of 0.2 %(w/v) of brimonidine tartrate. Around the priority date of the patent in suit it was known that this particular concentration led to serious side effects. Document (28) disclosed the expert recommendation that there should be a move to a product having a lower concentration of brimonidine tartrate in order to decrease the incidence and severity of allergic reactions (page 65, right column, middle of first paragraph). This was supported by the disclosure of document (9), which taught that the side effects of brimonidine tartrate were concentration-dependent. Document (50) proved that the product Alphagan®, containing 0.2 %(w/v) brimonidine tartrate, had almost immediately been replaced on the market by the newer product Alphagan® P, having 0.15 %(w/v) brimonidine tartrate, due to doctors favouring Alphagan® P. At the priority date of the patent in suit there was thus a prejudice against the use of higher concentrations of brimonidine tartrate. Such a prejudice had not existed before, e.g. when the studies for document (21) were carried out. Furthermore, the skilled person was aware that the fixing of a combination would probably aggravate the side effects known for the single actives. It was thus surprising that the fixing of the combination and the use of the 0.2 %(w/v) concentration of brimonidine tartrate led to a clinically significant reduction of the incidence rate of ocular allergies (see document (64)). Document (64) was not a direct

comparison with the closest prior art. It showed, however, that the fixing of the combination led to a reduction of ocular allergies. At the priority date the only means of reducing the ocular allergy rate was the reduction of the brimonidine concentration. The technical problem was the provision of a formulation for treating glaucoma that had good efficacy, improved safety and compliance and a reduction of the allergy risk as a side effect. No other document suggested the fixing of the combination of brimonidine tartrate and timolol maleate as the solution. There was thus an inventive step.

Auxiliary request 10A

The appellant argued that claim 1 of auxiliary request 10A, defining a BID dosage regimen and a specific composition, provided a considerable improvement over document (21) which was the closest prior art document. Documents (3) and (4) were farther removed than document (21) and document (31), which were roughly equivalent in content. Compared with the data shown in document (21), in tables 1 and 2 (page 41), the twice-daily administration of the fixed combination, in the composition now defined, led to a more constant lowering of intraocular pressure (IOP) during the course of the day. This more constant IOP reduction was shown on the first page 19 of document (61). This argument, although presented for the first time in oral proceedings before the board, was based on the most important effect addressed in the closest prior art document (21). Document (61), providing the data for the fixed combination, had been filed by the respondents during the opposition proceedings. The line of argument relating to constant IOP could therefore not come as a surprise to the respondents.

The appellant explained that claim 1 of auxiliary request 10A defined a very narrow, complete composition for a specific administration pattern. Reference was made to pages 35 to 37 of the statement of grounds of appeal. Of special importance was the surprisingly low level of benzalkonium chloride (BAK) preservative. The problem to be solved was the provision of a formulation for treating glaucoma that had good efficacy, improved safety and compliance and a reduction of eye irritation. A skilled person, being aware of eye irritation problems associated with BAK and in knowledge of the disclosure of document (28), page 65, right column, middle of first paragraph, would not have used BAK but 0.15 %(w/v) of Purite®, as in Alphagan® P. The closest prior art, document (21), would have suggested to the skilled person that a high concentration of preservatives was necessary. In document (21) the brimonidine-tartrate-containing composition comprised 0.005 % BAK, and the timolol maleate composition 0.01 % BAK, the sum being 0.015 %. The fact that a fixed combination using only 0.005 %w/v BAK, which was equivalent to one-third of the preservatives necessary in the closest prior art, was stable was thus a complete surprise to the skilled person. It can be seen from document (20) that different products, having different actives, require different BAK levels. It was thus clear for the skilled person that the BAK concentration was linked to the active, and a lowering of the BAK concentration consequently ran counter to what the skilled person would consider necessary. If a skilled person would not change the concentration of brimonidine tartrate in the closest prior art from 0.2 % to 1.5 % (see respondents' arguments on auxiliary request 4A), he would also not change the concentration of the preservatives of the

closest prior art. A lowering of the BAK would involve extensive research by the skilled person into the necessary BAK levels. Also, timolol-comprising compositions having entirely different further ingredients were known. The respondents had not shown that a skilled person would have arrived at the concrete composition defined in claim 1.

VIII. The respondents' arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Submissions relating to Article 55(1)(a) EPC

The submissions relating to Article 55 EPC were late filed. Document (28) had already been cited in opponent 5's notice of opposition as novelty-destroying disclosure and also in the context of inventive step. Also the opposition division had identified the document as relevant prior art. The appellant had thus been made aware of the relevance of document (28) in the opposition proceedings. It could, and should, have brought forward all the relevant facts, evidence and arguments concerning the alleged evident abuse at that stage already, thereby enabling the opponents to know its full case and to consider whether or not to maintain the objection based on this document. It should not be possible to hold back an argument because it was considered to have no chance of success. The opponents, now respondents, had been deprived of the opportunity to react in the opposition proceedings already to the allegations of an evident abuse. The evident abuse was not proven. All the evidence was in the hands of the proprietor. It was unclear, whether Dr Stamper had asked for permission to publish document (28), no declaration by Dr Stamper being on file, and

whether the information concerning the combination of timolol and brimonidine had even been obtained from the appellant. The respondents noted that no lawsuit had been initiated against Dr Stamper by the appellant.

Admission of auxiliary requests 4A and 10A

The auxiliary requests 4A and 10A had been filed at a very late stage of the appeal proceedings. Objections under Article 123(2) EPC had already been raised in the opposition proceedings from the beginning. Consequently, requests comprising amended claims should have been filed much earlier. Moreover, they were not suitable to straightforwardly overcome the issues, also because they were not accompanied by an adapted description.

Main request

Claim 1 of the main request lacked novelty in view of document (28). Document (28), in the context of glaucoma treatment (see title), disclosed a fixed combination of brimonidine and timolol (page 66, paragraph bridging the columns). Throughout document (28) the terms "brimonidine" and "brimonidine tartrate" and the terms "timolol" and "timolol maleate" were used interchangeably. This was also true for the rest of the literature, see e.g. documents (6) and (37). Also no other salts of brimonidine and timolol were approved by regulatory authorities.

With respect to inventive step the respondents disputed that the outcomes of the studies 024T (documents (42) and (62)) and 7831 (document (8)) could be combined in any way. The studies involved different collective patient groups, with e.g. differences in age. Also, the

7831 study was based on a self-assessment of the patients, which inevitably led to different results than an assessment by a physician. The 7831 study was in principle, due to its design, not a suitable source of evidence on the absence of side effects. In addition, as a general principle, a study based on the use of a single agent could not be combined with a study looking at combinations of active agents. Due to the influence of one active on the other a study dealing with a single active could in no way provide information suitable for the assessment of a study involving a combination of active ingredients. The analysis of the appellant was thus scientifically flawed. The decision T 1064/08 was not binding on the present board, since it related to examination proceedings. Also, the relevant material had not been made available in full to that board. The 507T study, which represented the correct comparison, did not show any effect of the fixing of the combination on somnolence. The expert declaration (66) provided some statements, qualified by terms like "appears to be" and "suggests to me", but did not provide a statistical analysis of the data. The technical problem to be solved lay in the provision of an alternative formulation containing the two actives leading to improved patient compliance. The fixing of the combination was known to be advantageous in terms of better patient compliance. This could be seen from documents (19), (28) and (32).

Auxiliary request 4A

The subject-matter of claim 1 of auxiliary request 4A had no further feature distinguishing it from the closest prior art, which already disclosed brimonidine tartrate in a concentration of 0.2 %w/v. By referring

to Alphagan® P the appellant had created an artificial further distinction. A prejudice could not be invoked since the majority of the commercially available products contained brimonidine tartrate in a concentration of 0.2 %(w/v) (see document (6)). The respondents further noted that the closest prior art document (21) had been published in January 2001, i.e. just before the priority date of the patent in suit. Document (64), which did not even show an effect of statistical relevance, was not a comparison with the closest prior art and therefore could not be taken into consideration. The same argument applied as for the main request.

Auxiliary request 10A

The respondents noted that the argument based on constant IOP had been raised for the first time on the second day of the oral proceedings before the board. It raised complex issues. Consultation of an expert and further research were necessary to deal with this argument. The argument based on constant IOP could not be dealt with during oral proceedings. Either it should not be admitted or the oral proceedings should be adjourned.

Claim 1 of auxiliary request 10A defined a concrete composition comprising only ingredients which were well known in the field of treating glaucoma. The two actives in their respective concentrations were known from the closest prior art. BAK, buffers, acidifying and basifying agents and water were the usual components of such compositions. There was no evidence on file that the composition of claim 1 led to any improvement. In document (20), page 207, published only five months before the priority date of the patent in

suit, the preservatives of several commercially available products were listed. It could be seen from this list that the concentration of 0.005 % BAK was not unusual. It could also be seen that fixed combinations did not have higher concentrations of preservatives than mono-formulations. Furthermore it was a routine approach for a skilled person to start with a low concentration of BAK for testing. Also for timolol-containing formulations various concentrations of BAK were known (documents (6) and (56)). It was thus obvious for the skilled person to combine the various well-known ingredients at well-known concentrations and carry out routine testing. The skilled person would thus arrive at the now claimed composition without having to exercise any inventive skill.

IX. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request as filed together with the statement of grounds of appeal or, alternatively, on the basis of one of the sets of claims filed as auxiliary requests 4A and 10A with the letter dated 17 March 2017. Furthermore, it requested that the board refer questions to the Enlarged Board of Appeal on the interpretation of Article 55 EPC.

Respondents 1, 2, 3, 5 and 6 requested that the appeal be dismissed and that auxiliary requests 4A and 10A not be admitted into the proceedings. Furthermore, respondents 1, 5 and 6 requested that the facts and arguments put forward in connection with the evident abuse within the meaning of Article 55 EPC, and related document (65), not be admitted into the proceedings. Respondents 1 and 2 further requested that no referral be made to the Enlarged Board of Appeal.

Respondent 4 had no requests in appeal.

Reasons for the Decision

1. The appeal is admissible.

2. Oral proceedings were held and continued in the absence of the duly summoned respondent 4 in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

3. *Admission of auxiliary requests 4A and 10A*

Auxiliary requests 4A and 10A were admitted into the proceedings in accordance with Article 13(1) and (3) RPBA. As compared with the corresponding claim requests previously on file, i.e. auxiliary requests 4 and 10 underlying the decision under appeal, which were re-filed by the appellant together with the statement of grounds of appeal, they contained amendments that were intended to overcome issues under Article 123(2) EPC addressed by the board in its communication under Article 15(1) RPBA. These amended sets of claims did not raise any complex issues and were filed about three months prior to the oral proceedings before the board, i.e. at a stage of the proceedings at which it could be expected that the other parties could deal with the changed situation and properly prepare their counter-arguments. That no adapted description for these claim sets submitted as auxiliary requests 4A and 10A was on file might have led to a finding that, on a *prima facie* basis, the requirements of Article 84 EPC were not met. However, the board considered that this circumstance could not weigh against the appellant, since the decision of the opposition division was not based on the aspect of an

adapted description being absent and the board had given the appellant no reason to believe that, at that stage of the appeal proceedings, it would be unacceptable to file amended sets of claims only and postpone the filing of one or more adapted descriptions.

4. *Admission of submissions relating to Article 55(1)(a) EPC*

4.1 In accordance with Article 12(4) RPBA, the board has the discretion to hold inadmissible facts, evidence or requests which were presented in the statement of grounds of appeal, but which could have been presented in the first instance proceedings.

4.2 With the statement setting out its grounds of appeal the appellant, for the first time, requested that document (28) be disregarded, since its disclosure was due to an evident abuse within the meaning of Article 55(1)(a) EPC. In this context the appellant also requested a re-referral to the Enlarged Board of Appeal. In the appellant's view the Enlarged Board, in its decision G 3/98 (OJ EPO 2001, 62), erroneously established that, for the calculation of the six-month period referred to in Article 55(1)(a) EPC, the relevant date was the date of the actual filing of the European patent application, and not the priority date.

4.3 The submissions in relation to Article 55(1)(a) EPC were not presented before the opposition division, although document (28) had been filed by opponent 5, now respondent 5, with its notice of opposition of 9 October 2013 and, throughout the opposition proceedings, document (28) was considered to be highly pertinent. Moreover, all the evidence filed by the

appellant in support of the alleged evident abuse lay within its own knowledge and sphere and had already been available to it when document (28) was first cited in the opposition proceedings. Accordingly, the board cannot see any reason which could have prevented the appellant from already presenting its submissions concerning an evident abuse during the opposition proceedings.

4.4 The appellant has argued that it did not bring the issue up in front of the opposition division because an opposition division cannot refer questions to the Enlarged Board of Appeal. A further referral would however be necessary in order for the Enlarged Board's previous decision G 3/98 relating to the interpretation of Article 55(1)(a) EPC to be overturned.

In this respect the board notes that the question of a (re-)referral would arise in relation to only one of the prerequisites of Article 55(1)(a) EPC, namely the calculation of the six-month time period. However, other requirements too would have to be met for a disclosure to be disregarded pursuant to Article 55(1)(a) EPC. In particular, it would have to be established whether the alleged evident abuse in relation to the appellant or his legal predecessor is to be considered proven.

The appellant was of the view that the opposition division would, on the basis of the decision G 3/98, have rejected the argument under Article 55(1)(a) EPC due to the publication date of document (28) lying outside the six-month period, and would not have decided on the allegations of the evident abuse.

How the case would have been handled by the opposition division if the submissions had been presented earlier is a matter of pure speculation. In any case, had the issue already been addressed in opposition proceedings, the opponents would have been informed that document (28) might not be taken into consideration as prior art and they could have considered whether or not to focus on a disclosure which uncontroversially constituted prior art rather than on document (28).

Instead, the respondents were confronted with the fact that document (28) might not be taken into consideration for the first time in appeal proceedings.

4.5 In addition, taking the appellant's submissions concerning the evident abuse into consideration by the board would have resulted in entirely new aspects being discussed for the first time at the appeal stage. That would not be in line with the purpose of the *inter partes* appeal procedure, which is mainly to give the losing party an opportunity to challenge the decision of the opposition division on its merits.

4.6 Even though the foregoing considerations were, in the board's view, sufficient reason to decide that the submissions concerning an evident abuse under Article 55(1)(a) EPC, and the related evidence, should not be considered at the appeal stage, the board has also taken into account whether the proprietor's submissions and evidence were highly relevant and would constitute a clear-cut case.

While the appellant considered the evident abuse clearly established, the respondents questioned the scope of the confidentiality obligations, the sources of information Dr Stamper had used when he wrote the

disclosure of document (28), and the absence of permission from the appellant to publish document (28).

Article 7 of the "Physician Consultant Agreement" contained in document (65) does mention the possibility of giving Dr Stamper permission to publish information falling under the confidentiality agreement. The question has been raised whether Dr Stamper asked for such a permission. The appellant has asserted that Dr Stamper did not do so. The respondents have countered that neither is any declaration by Dr Stamper on file nor is there evidence of a civil suit of the appellant against Dr Stamper.

As can be seen from the above, various issues were in dispute and remained unclear on the basis of the evidence filed by the appellant.

4.7 In summary, the submissions in relation to Article 55(1)(a) EPC could have been presented during opposition proceedings. The submissions involve a complex discussion of issues that should have been addressed in opposition proceedings and could possibly have led to a change in the opponents' cases. Furthermore, considering the respondents' arguments brought forward in relation to the evidence provided by the appellant, the board could not straightforwardly establish that an evident abuse in relation to the appellant had actually occurred.

4.8 In view of the above and in exercise of its discretion under Article 12(4) RPBA, the board decided not to admit the appellant's submissions that the disclosure of document (28) had been an evident abuse in relation to the appellant according to Article 55 (1)(a) EPC,

and the related evidence in the form of document (65), into the appeal proceedings.

As a consequence, the appellant's request for a referral to the Enlarged Board of Appeal was no longer relevant.

5. Document (66)

Document (66) was filed together with the statement setting out the grounds of appeal and thus forms part of the appellant's case under Article 12(1) RPBA. The document is an expert declaration and as such was filed to shed light on certain points of the impugned decision. It can be regarded as a legitimate reaction to the decision under appeal because the content is closely related to the issues addressed in the decision. The board therefore admitted it into the appeal proceedings under Article 12(4) RPBA.

Main request

6. Novelty

Document (28) discloses that a combination of brimonidine and timolol is being studied and may become available soon (page 66, right column, first paragraph).

The respondents have argued that all other parts of document (28) clearly relate specifically to brimonidine tartrate and timolol maleate and that furthermore no other salts of brimonidine and timolol have been approved by regulatory authorities. All the mono-formulations on the market comprise either

brimonidine tartrate or timolol maleate (see documents (6) and (37)).

However, the passage referring to said study on page 66 in document (28) does not directly and unambiguously disclose which brimonidine and timolol compounds are "being studied". It is possible that either the free bases or other salts of the actives are used in the study. Neither other parts of document (28) nor any other disclosures not directly relating to said study can be relied on to unambiguously prove the form in which brimonidine and timolol were used in said study.

The subject-matter of claim 1 of the main request therefore differs from the combination disclosed in document (28) in that it specifically defines the salts of brimonidine and timolol used.

There is no need to discuss whether the technical feature of the treatment of glaucoma is disclosed in the relevant passage of document (28).

The subject-matter of claim 1 of the main request is new (Article 54 EPC).

7. *Inventive step*

7.1 The present invention is directed to an ophthalmic pharmaceutical formulation in the form of a fixed combination of brimonidine tartrate and timolol maleate for use in the treatment of glaucoma and ocular hypertension. The ophthalmic formulation should be effective and safe, have increased stability and require a lower effective concentration of preservative as compared to the individual agents taken alone. Concerns about patient compliance should also be

overcome (patent in suit, paragraph [0001]). Among the safety aspects, somnolence and allergic conjunctivitis are mentioned (page 8, table).

7.2 Closest prior art

In the contested decision and in the respondents' replies to the grounds of appeal two different lines of argument have been brought forward. In the first one, document (28) is considered to present the closest prior art, the second starts from the disclosure of any of documents (3), (4), (21) and (31) as the closest prior art.

In view of the outcome of the assessment of inventive step when starting from any of documents (3), (4), (21) and (31), the line of argument based on document (28) as the closest prior art does not need to be discussed.

In the discussion of auxiliary request 10A the appellant has voiced reservations concerning the suitability of documents (3) and (4) as the closest prior art. Document (21), however, has been considered by all parties to represent one possible closest prior art document.

Document (21) defines as its purpose the evaluation of the additive ocular hypotensive effect of the combination of brimonidine and timolol on intraocular pressure (IOP) reduction in patients with glaucoma (abstract, first paragraph). In the treatment period timolol maleate 0.5 % and brimonidine tartrate 0.2 % or timolol maleate 0.5 % and a placebo were applied sequentially twice daily (page 40, left column, last two paragraphs). For the application of timolol maleate the commercially available product "Cusimolol"® was

used, for the application of brimonidine tartrate "Alphagan"® was used (page 40, right column, first paragraph). In the results section it is stated that both medications were well tolerated and no adverse effects led to discontinuation of use (page 41, left column, first paragraph).

The difference between claim 1 of the main request and the disclosure of document (21) is thus the formulation of brimonidine tartrate and timolol maleate as a fixed combination.

7.3 *Technical problem*

The appellant sees the technical problem in the provision of a formulation for treating glaucoma that has good efficacy and improved safety and compliance.

The board notes that the appellant has questioned the legal standard to be applied when assessing data in order to establish the presence of effects. In this respect reference is made to the Case Law of the Boards of Appeal of the European Patent Office ("CLBA"), 8th edition 2016, chapter I.D.4. Here the problem and solution approach is discussed in the context of established case law. The board followed especially the principles set out in chapter I.D.4.1 establishing the criteria for comparisons with the closest prior art. There it is stated that where comparative tests are chosen to establish inventive step on the basis of an effect produced over the claimed area, the comparison with the closest prior art must show convincingly that the effect was attributable to the feature distinguishing the invention. The aim of such a comparison is to demonstrate that the technical effect

has its **exclusive origin** in the feature characterising the invention in the claims.

According to the appellant the fixing of the combination results in a reduction of somnolence. In this context it referred to two studies, 024T and 7831:

Study 024T is a clinical study comparing BID administration of a fixed combination of brimonidine tartrate and timolol maleate with the sequential administration comprising BID administration of timolol maleate and TID administration of brimonidine tartrate. There is a first arm in which twice daily, at hours 0 and 12, one dose of a formulation comprising only the vehicle and one dose of a formulation comprising brimonidine tartrate and timolol maleate was administered to the eye; at hour 6 only the vehicle was administered. In a second arm of the study, twice daily, at hours 0 and 12, two doses of medication were applied, one comprising brimonidine tartrate, the second comprising timolol maleate, and additionally a third dose, at hour 6, of brimonidine tartrate was given. The two administrations at hours 0 and 12 were at least 5 minutes apart (document (53), page 9, table 1). The primary end point of this study is the proportion of sleepiness responders, assessed using the Stanford Sleepiness Scale. Documents relating to the 024T study are documents (42), (53), (60), (62) and (69).

Study 7831 is a clinical study having as its aim an assessment of safety and efficacy and comparing TID administration of brimonidine tartrate with BID administration of brimonidine tartrate. One drop of the formulation comprising brimonidine tartrate was instilled in the morning (between 7:00 and 9:00 a.m.),

one drop of the brimonidine tartrate composition or one drop of vehicle (for the BID group) in the afternoon (between 2:00 and 3:00 p.m.) and one drop of the brimonidine tartrate composition in the evening (between 10:00 p.m. and 12:00 a.m.), these times corresponding roughly to hours 0, 7 and 15 (document (8), page 19, chapter 4.5.3).

The appellant has argued that the outcome of study 024T, that the fixed combination led to a reduced proportion of current severity of sleepiness responders, and the outcome of study 7831, that TID and BID administration of brimonidine tartrate led to the same level of fatigue/drowsiness, could logically be combined.

According to the appellant the surprising effect of the invention lies in the fact that the fixed combination has a lower level of adverse side effects in the form of somnolence than the pharmaceutical actives administered separately, due to drug interaction.

If, however, the effect is due to drug interaction, the outcomes of the two studies cannot be combined.

Study 024T examines, on the one hand, the effects due to any possible interaction of the two actives, and on the other, the effects due to sequential administration of the two actives plus the action of the brimonidine tartrate administered alone. Study 7831 provides information on one single agent, brimonidine tartrate. It is questionable whether the influence of one active on another can be assessed, when one of these actives is additionally administered in a single application. On the other hand, it also cannot be excluded that said active, administered in a further single application,

is not influenced in its activity by the preceding administration of the two actives, in which case it stands to reason that the morning and evening doses of the brimonidine tartrate do not necessarily act in the same way as the mono-dose in study 7831. Likewise, a study assessing the effects of administration of a single active cannot provide information applicable to a study where said single active is (partly) administered in combination with another active.

Furthermore, there are major differences between study 024T and study 7831. They differ in patient groups, run-in regimen, duration and administration scheme. The most important point, however, seems to be the way of eliciting information on the side effects from the patients. In study 024T the proportion of sleepiness responders was a primary end point, involving a dedicated form relating to the Stanford Sleepiness scale to elicit the required information from the patients. In study 7831 symptoms of discomfort were elicited by directed questioning of the patients. The actual questions posed led to answers related to fatigue, somnolence and drowsiness. It is uncertain whether the reported effects of study 024T can be compared with the effects obtained by study 7831.

The appellant has filed the expert declaration (66). Mr Davis, an expert in statistical aspects of clinical trials, states that he derives from study 7831 that the additional dose of brimonidine in the concurrent arm of study 024T "is likely not a significant confounding variable" (document (66), page 5, first paragraph). Document (66) does not address the boards main concern, i.e. that there is a problem of principle when applying information gained from a study not having any drug-drug interactions to a study aiming at proving an

effect due to a drug-drug interaction. Since document (66) is silent on the effects of possible drug-drug interactions, it cannot overcome the board's main concern in relation to the two studies.

In summary, the outcomes of the two studies cannot be combined, and consequently no comparison with the closest prior art has been provided. The effect of reduced somnolence thus cannot be linked to the distinguishing technical feature and must be disregarded when following the problem and solution approach.

The board further notes that decision T 1064/08 has no binding effect for the present case. It is established case law (see e.g. T 167/93, OJ EPO 1997, 229) that decisions stemming from the appeal against a decision of the examining division, i.e. from an ex-parte case, are not binding for appeals stemming from a decision issued by an opposition division, i.e. an inter-partes case.

Since the technical effect of reduced somnolence cannot be taken into account, the technical problem has to be reformulated.

The technical problem can be seen as the provision of means of administering a combination of brimonidine tartrate and timolol maleate leading to better patient compliance.

None of the parties has contested that the problem of improved compliance has been solved. The board also considers the problem to be solved.

7.4 *Obviousness*

The provision of fixed combinations having two active pharmaceutical ingredients in the treatment of glaucoma is known in the art. Also, fixed combinations are said to address patient compliance issues.

Document (28) states, in the context of the fixed combination "Cosopt®", that "by combining two medications into one bottle compliance should be improved" (page 66, left column, first paragraph). Document (32), page 423, left column, second full paragraph, discloses that "the convenience factor for patients is quite compelling" and that an advantage can be derived for a manufacturer providing a fixed combination by gaining "additional market share if patients remain on their products as therapy is advanced".

When striving for improved compliance, the formulation of two pharmaceutical active agents as a fixed combination is therefore an obvious solution for a skilled person.

7.5 Consequently, the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

In view of the board's conclusions on inventive step in relation to the main request, study 507T, which was relied upon by the respondents in order to support their argument that an effect of the fixing of the combination on somnolence was not shown, does not need to be addressed.

Auxiliary request 4A

8. Inventive step

Claim 1 of auxiliary request 4A differs from claim 1 of the main request in that the use is defined as being topical and concentrations of brimonidine tartrate and timolol maleate are defined. The reasons set out under points 7.1 and 7.2 in relation to the main request still apply.

With respect to the last paragraph of point 7.2 above, the board notes that there is a further difference between the disclosure of document (21) and the subject-matter of claim 1 of auxiliary request 4A. While claim 1 of auxiliary request 4A defines the concentration of timolol maleate as 0.68 %(w/v), document (21) describes the use of "timolol maleate 0.5 %" (abstract; page 39, right column, last sentence of paragraph 3; page 40, left column, paragraph 4). Document (21) uses timolol in form of the commercially available product Cusimolol®, whose ingredients have not been discussed (page 40, right column, first paragraph).

8.1 Technical problem

The appellant sees the technical problem in the provision of a formulation for treating glaucoma that has good efficacy and improved safety and compliance.

According to the appellant the fixing of the combination and the use of 0.2 %(w/v) of brimonidine tartrate results in a reduction in the incidences of ocular allergies. In this context it referred to document (64).

Document (64) has as its objective to evaluate the incidence of ocular allergy in glaucoma patients and compares the incidence rates of 0.2 % brimonidine monotherapy to therapy with the fixed combination of brimonidine 0.2 % and timolol 0.5 % (abstract). As can be seen from the results section, especially from figure 1, the percentage of patients who developed an ocular allergy was lower for those receiving the fixed combination than for those on monotherapy. The results are said to be clinically significant.

Document (64) does not provide a comparison that is relevant for the subject-matter claimed here. According to established case law, see CLBA, cited above, chapter I.D.4.1., a comparison with the closest prior art has to show convincingly that the effect is attributable to the feature distinguishing the invention. When, as in the present case, the comparison is effected against a formulation that is farther removed from the claimed subject-matter than the closest prior art formulation, any determined effects cannot be attributed to the distinguishing feature and consequently cannot be taken into account.

The appellant has argued that document (64) was not cited as a comparison with the closest prior art. According to the appellant document (64) shows that the fixing of the combination is a new way of reducing incidents of ocular allergy which was not known at the priority date of the patent in suit. Then, only the reduction of the brimonidine concentration was suggested. However, this line of argument does not change the European Patent Office's problem and solution approach (see CLBA, cited above, chapter I.D.2.): Any effect invoked has to be established as

due to the feature constituting the difference over the closest prior art.

The effect of reduced incidence of ocular allergies thus cannot be linked to the distinguishing technical feature and will be disregarded when following the problem and solution approach.

Since the technical effect of reduced incidence of ocular allergies cannot be taken into account, the technical problem has to be reformulated.

The technical problem can be seen as the provision of means of administering a combination of brimonidine tartrate and timolol maleate leading to better patient compliance.

None of the parties has contested that the problem of improved compliance has been solved. The board also considers the problem to be solved.

8.2 *Obviousness*

The same reasons as given under point 7.4 in relation to the main request also apply to claim 1 of auxiliary request 4A.

The parties have not directed their arguments to the concentration of timolol maleate. The board notes that the concentration of timolol maleate of 0.68 %(w/v) lies within the usual concentration ranges (document (6), references 67143, 67146, 67147 and 67155; document (56), e.g. reference 67159) and is thus an obvious concentration for the skilled person.

8.3 The subject-matter of claim 1 of auxiliary request 4A does not involve an inventive step (Article 56 EPC).

8.4 Further arguments

The appellant has argued that around the priority date of the patent in suit there was a prejudice against the use of brimonidine in concentrations of 0.2 %(w/v).

It is true that document (28) teaches that a lower concentration of brimonidine may decrease the incidence of allergic reactions and refers to the product Alphagan® P, which has a brimonidine tartrate concentration of 0.15 %(w/v) (document (28), page 65, right column, middle of first paragraph; document (51), page 1). However, most other documents relating to brimonidine show that at the priority date of the patent in suit brimonidine tartrate at a concentration of 0.2 % was being marketed or investigated (e.g. document (3), "Objectives"; document (4), abstract; document (6), reference 67157; document (31), "Purpose"). The board further notes that a brimonidine tartrate concentration of 0.2 % was also used in document (21), discussed as the closest prior art and starting point of the problem and solution approach. Documents (21) and (28) were both published at the beginning of 2002. A single disclosure does not establish a prejudice that would lead a person skilled in the art to disregard the information found in the closest prior art. No substantiated reasons have been provided to explain why Alphagan® P has increased its market share over Alphagan®. Various reasons, some not linked to the number of side effect incidences, seem to be possible. The market share of Alphagan® P therefore cannot be seen as teaching away from the use of 0.2 %(w/v) brimonidine tartrate in a fixed combination.

Auxiliary request 10A

9. Inventive step

Claim 1 of auxiliary request 10A differs from claim 1 of the main request in that the use is defined as being topical, the composition is for twice-daily administration and the composition consists of the ingredients listed in the table of claim 1 of auxiliary request 10A. The reasons given under point 7.1 and 7.2 in relation to the main request still apply.

9.1 Technical problem

The appellant sees the technical problem in the provision of a formulation for treating glaucoma that has good efficacy and improved safety and compliance.

9.1.1 *Admission of appellant's first line of argument*

The appellant first of all presented a new line of argument based on the effect of achieving a constant IOP suppression over the day, based on data disclosed in document (61). According to the appellant an improvement is seen over the data presented in the closest prior art in the form of document (21).

Auxiliary request 10A differs from auxiliary request 11, first filed during the opposition proceedings on 9 June 2015, only in the introduction of the term "topical", replacing the definition "topical administration of the composition to the eye", deletion of the terms "ocular hypertension", while "glaucoma" was retained, and a slight rewording of the claim. The opposition division's decision dealt with the treatment

of glaucoma by twice-daily administration and considered only documents disclosing topical administration, i.e. a factual situation very similar to that addressed in auxiliary request 10A.

The appellant did not invoke the effect of constant IOP in the opposition proceedings. Also, neither the statement of grounds of appeal nor the letter dated 17 March 2017, accompanying the filing of auxiliary request 10A, mentions constant IOP. The line of argument based on the effect of achieving constant IOP suppression over the day was not relied upon until the second day of the oral proceedings on appeal.

The respondents, apart from considering the line of argument to be late filed, have indicated that they were not in a position to deal with this line of argument in the oral proceedings. Expert consultation and possibly a further search were deemed to be necessary.

Document (21) comprises two tables, table 1 and table 2, listing the IOP or its reduction at 3 points in time over the day for week 1, week 2 and week 3 of the treatment. Document (61) had been filed by respondent 2 in the opposition proceedings. On the first page, numbered 19, it depicts a table relating to a "190342-012T" study. This study, however, had neither been considered in the decision under appeal nor been addressed by any of the parties or the board during the appeal proceedings. The argument was thus presented at the latest possible stage of the appeal proceedings. The table on page 19 shows mean IOP at four points in time over the day for week 2, week 6, month 3, month 6, month 9 and month 12 of the treatment. A comprehensive set of data has to be evaluated and to be assessed in

the context of the problem and solution approach. Such a complex task goes beyond what can be reasonably undertaken during oral proceedings.

Therefore, the board, exercising its discretion under Article 13(1) RPBA, decided not to admit this line of argument into the appeal proceedings.

9.1.2 Appellant's second line of argument - BAK

The appellant also pointed to the specific formulation defined in claim 1 of auxiliary request 10A. It especially stressed the use of benzalkonium chloride (BAK) as preservative and its low concentration, i.e. at 0.005 %(w/v). According to the appellant it is surprising, in view of document (21) using 0.005 % BAK in the Alphagan® product and 0.01 % BAK in the timolol-maleate-containing product, that such a low amount of preservative, which is only about one-third of the sum of the closest prior art, leads to safe and efficacious formulations having surprisingly little side effects.

The appellant formulated the technical problem to be solved as the provision of a formulation for treating glaucoma that has good efficacy and improved safety and compliance. Eye irritation especially was lessened by the reduction in the concentration of BAK.

Starting from document (21) there are thus two issues to be addressed. The first is the fixing of the combination. Reference is made to the board's reasoning concerning the main request and auxiliary request 4A, which applies equally to the subject-matter claimed here, since the amount and type of preservative is not generally linked to patient compliance, which has been discussed in the context of the number of necessary

administrations of formulations over the day and not in the context of side effects.

The second issue, after finding the fixing of the combination to be obvious, are the actual ingredients and their concentrations in the formulation comprising the fixed combination, especially the type and amount of preservative used and the pH of the final composition.

It is a generally accepted principle that the level of preservative should be kept as low as possible, while still achieving the required stabilisation. This is reflected in the introductory passages of document (20).

Table 1 of document (20) lists various ophthalmic solutions and the type and amount of preservative contained therein. Both Alphagan®, comprising brimonidine tartrate and 0.005 % BAK, and Alphagan® P, comprising brimonidine tartrate and 50 ppm SOC (Purite®), are listed. As an example of a fixed combination, Cosopt®, containing dorzolamide hydrochloride, timolol maleate and 0.0075 % BAK, is given. Timolol-maleate-based formulations are Timoptic®, containing 0.01 % BAK, and Timoptic-XE®, containing 0.012 % benzododecinium bromide. From this table it can be concluded that, while BAK is the predominantly used preservative, several preservatives are used in ophthalmic solutions and that the concentrations vary from 0.005 % to 0.02 %, irrespective of whether there are one or two active agents in the formulation. Document (6) provides information on several eye drops containing timolol maleate as active agent. Reference 67143 relates to various concentrations of timolol maleate, one

containing 0.005 %(w/v) BAK together with sorbitol, polyvinyl alcohol, carbomer and an acetate-based buffer, another one containing disodium hydrogen phosphate, sodium dihydrogen phosphate and 0.003 %(w/v) BAK, and one formulation not containing preservatives. Document (56), under reference 67159, discloses a composition comprising timolol maleate, disodium hydrogen phosphate, sodium dihydrogen phosphate and 0.005 %(w/v) BAK. In summary it can be seen that various preservatives, BAK being a frequent one, at various concentrations are used in the art. Mono- and combination-formulations have similar concentrations of preservatives.

The technical problem to be solved may be defined as the provision of an actual safe and effective formulation for the fixed combination of the two active ingredients under consideration.

The solution proposed by the subject-matter defined in claim 1 of auxiliary request 10A consists in the selection of specific ingredients, i.e. the preservative and the type of buffer, and their amounts. The problem has been solved. This has not been contested.

The skilled person, faced with the task of providing an actual ophthalmic pharmaceutical composition comprising two known active pharmaceutical ingredients, will look for guidance in the prior art, especially in documents relating to actual formulations comprising either brimonidine tartrate or timolol maleate. When deciding on which formulation to test first, the skilled person would stick as closely as possible to ingredients and conditions already approved for the mono-products, while keeping the amount of preservative as low as

possible. As the appellant has stated in its statement of grounds of appeal, on page 36, first paragraph, Alphagan® P comprises brimonidine tartrate with a pH of 7.2, Alphagan® 0.2 %(w/v) brimonidine tartrate with a pH of 6.3-6.5 and Timoptic® timolol maleate with a pH of 7.0. A skilled person would thus carry out routine tests in the pH range of 6.3 to 7.2 when trying to find the optimal pH for the fixed formulation. On the same page, third paragraph, the buffer of the Alphagan® products is said to be a citric acid buffer system, while Timoptic® uses a phosphate buffer system. The skilled person would thus test these two buffer systems. Alphagan® P uses a Purite® preservative, Alphagan® 0.005 %(w/v) BAK and Timoptic® 0.01 %(w/v) BAK. Starting with the preservative known to be suitable for both actives, i.e. BAK, is obvious for the skilled person when performing routine tests. In view of the above established link between eye irritation and the use of BAK, a person skilled in the art would first investigate whether the required stability could be achieved by the lower concentration. In conclusion, the board considers that a limited number of routine tests would lead the skilled person in an obvious way to the formulation defined in claim 1 of auxiliary request 10A.

9.2 Therefore, the subject-matter of claim 1 of auxiliary request 10A does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated