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**Datasheet for the decision
of 25 September 2018**

Case Number: T 0099/14 - 3.3.01

Application Number: 02739579.7

Publication Number: 1392319

IPC: A61K31/5575, A61K31/535,
A61K45/06, A61P27/06

Language of the proceedings: EN

Title of invention:

HYPOTENSIVE LIPID (PROSTAGLANDIN) AND TIMOLOL COMPOSITIONS AND
METHODS OF USING SAME

Patent Proprietor:

ALLERGAN, INC.

Opponents:

Alfred E. Tiefenbacher (GmbH & Co. KG)
RAFARM Commercial and Industrial Company of
Pharmaceutical Products
Societe Anonyme (RAFARM S.A.)
Aspire Pharma Limited

Headword:

Bimatoprost and Timolol/ALLERGAN

Relevant legal provisions:

EPC Art. 54, 56, 100(a), 100(b)

Keyword:

Novelty - (yes)

Inventive step - (yes)

Insufficiency of disclosure (no)

Decisions cited:

G 0001/03, T 0967/09



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Case Number: T 0099/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 September 2018

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on
17 December 2013 rejecting the opposition filed
against European patent No. 1392319 pursuant to
Article 101(2) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 1 392 319 is based on European patent application No. 02739579.7, filed as an international application published as WO2002/096432.

II. The patent as granted has two independent claims, claim 1 and claim 6. They read as follows:

"1. Use of a composition comprising:

(i) a timolol component present in an amount effective to reduce ocular hypertension when applied to a hypertensive eye; and

(ii) a hypotensive lipid component present in an amount effective to reduce ocular hypertension when applied to a hypertensive eye,

for the preparation of a medicament for use in treating ocular hypertension,

said hypotensive lipid component comprising:

cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3, 5-dihydroxy, [1 α , 2 β , 3 α , 5 α]."

"6. A composition comprising:

(i) a timolol component present in an amount effective to reduce ocular hypertension when applied to a hypertensive eye; and

(ii) a hypotensive lipid component present in an amount effective to reduce ocular hypertension when applied to a hypertensive eye, said composition when applied to an eye being effective to treat ocular hypertension, the hypotensive lipid component comprising:

cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 α , 2 β , 3 α , 5 α]."

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

(2) EP-A-509 752

(3) WO98/25620

(4) EP-A-286 903

(5) EP-A-590 972

(6) EP-A-458 590

(7) Cantor, *Exp Opin Invest Drugs*, 2001, 10(4), 721-731

(9) US 5,688,819

(10) WO00/04898

(20) WO00/54810

(24) Larsson, *Acta Ophthalmol Scand*, 2001, 79, 125-128

(33) Lewis et al., *J Glaucoma*, 2010, 19(6), 424-426

(34) Brandt et al., *J Glaucoma*, 2008, 17(3), 211-216

(40) Katsanos et al., *J Ocul Pharmacol Ther*, 2011, 27(1), 67-71

(41) Chen et al., *Cardiovasc Drug Rev*, 2005, 23(3), 231-246

(42) WO2013/163219

(44) Bartlett and Jaanus (editors), *Clinical ocular pharmacology*, 3rd edition, 1995, 183-231

(45) Lewis and Fingeret (editors), *Primary care of the glaucomas*, 1993, 245-249

(46) Mauger and Craig (editors), *Havener's ocular pharmacology*, 1994, 84-112

(47) Hommer, *Europ J Ophthalmol*, 2007, 17(1), 53-62

(52) LumiganTM, NDA 21-275, March 2001, 1-6

- IV. Opponent 1 (appellant) lodged an appeal against the decision of the opposition division to reject the oppositions.
- V. By letter dated 31 January 2018, notice of intervention in the proceedings under Article 105 EPC was filed by Aspire Pharma Limited (opponent 3).
- VI. In a communication pursuant to Article 15(1) RPBA, the board informed the parties of its preliminary opinion on some of the issues at stake. Oral proceedings were held before the board on 25 September 2018 in the absence of opponent 2 (party as of right).
- VII. The appellant's and opponent 3's ("opponents'") arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Sufficiency of disclosure

The construction of a particular claim should be identical for the assessment of inventive step and sufficiency of disclosure, i.e. the same invention had

to be assessed under Articles 56 and 83 EPC (see T 967/09). The reduction of hyperemia due to the addition of timolol to bimatoprost had not been mentioned in the application as filed, let alone been made plausible at the filing date of the patent in suit.

Furthermore, it was not plausible per se that the hypotensive effects of a combination of timolol and bimatoprost at any concentration always provided sufficient lowering of intraocular pressure. In this respect, it was noted that the combined effect obtained by the combination of the two actives was slightly less than additive and consequently no sufficient lowering of intraocular pressure was to be expected at the lower concentration ends described in the application as filed (see the table in paragraph [0043] of the patent).

Novelty

Document (10) defined an ophthalmic formulation for the treatment of ocular hypertension and glaucoma comprising, inter alia, a β -adrenergic antagonist and a prostaglandin, prostaglandin derivative, or a hypotensive lipid derived thereof. Timolol was mentioned on page 5, line 27, as one of two preferred β -adrenergic antagonists, the other being betaxolol. The examples relied exclusively on two β -adrenergic antagonists, timolol and metipranolol. Since timolol was mentioned in both passages it was clearly the most preferred β -adrenergic antagonist, no selection was thus necessary. A single selection, the selection of AGN 192024 (another name for bimatoprost) as a prostaglandin, prostaglandin derivative or hypotensive lipid derived thereof led to the subject-matter of

claims 1 and 6. The disclosure of document (10) was thus novelty-destroying.

Inventive step

The treatment of ocular hypertension might require the use of a combination of active agents. It was well established in the state of the art that when the administration of one active did not lead to a sufficient reduction of intraocular pressure, a second active with a different mechanism of action was added to the treatment scheme. A skilled person would have considered only two basic mechanisms, the reduction of aqueous humour inflow, and the increase of aqueous humour outflow. Considerations about which receptor led to which mechanism were not pertinent for the selection of the second active. Furthermore, a skilled person would have considered bimatoprost to belong to the general class of prostaglandin-derived actives. A first indication lay in the similarity in molecular structure. A second indication came from the prior art. Document (9) clearly presented bimatoprost as a further development of prostaglandins and prostaglandin derivatives, such as PGF₂ α isopropylester and latanoprost (column 2, lines 34 to 49). Bimatoprost would thus have been seen as a modern, prostaglandin-derived active. Furthermore, document (42), a patent application by the proprietor of the present patent in suit, acknowledged that the same class effects arose with latanoprost and bimatoprost, both prostaglandins.

Two separate approaches were relevant for the assessment of inventive step, starting, respectively, from a combination therapy or a mono-therapy of bimatoprost as the closest prior art.

Two documents could be seen as the closest prior art for the combination therapy approach, documents (4) and (24). Document (4) disclosed a combination of PGF2 α isopropylester and timolol, teaching that this combination allowed for reduced concentrations of the actives and led to lower side effects (claims and column 3, lines 26 to 34). Document (24) related to a combination of latanoprost and timolol (abstract). The difference between the claimed subject-matter and these documents was the replacement of the prostaglandin derivative with bimatoprost. No effect due to this difference had been shown. The technical problem was thus the provision of an alternative combination. Since it was known - from, for example, document (9) - that bimatoprost was a further, improved development for both PGF2 α isopropylester and latanoprost, it was obvious to use it as a replacement (see document (9), column 3, line 13 to 19).

In the case of the mono-therapy, either document (7), (9) or (52) could be seen as the closest prior art. Document (7) described that bimatoprost on its own was capable of providing a safe and effective treatment, although conjunctival hyperaemia was mentioned as side effect. Document (9), providing a teaching that was almost word-for-word identical to the patent in suit, taught that the class of compounds to which bimatoprost belonged, including, specifically, bimatoprost, had considerably reduced side effects compared with known hypotensive prostaglandin PGF2 α derivatives. The possibility of combinations was disclosed in column 11, lines 49/50. Document (52) described bimatoprost as a prostamide capable of increasing outflow of aqueous humour through both the trabecular meshwork and uveoscleral routes. It was explicitly mentioned that

bimatoprost was a "synthetic structural analog of prostaglandin" (see "Mechanism of Action"). The concomitant use with other topical ophthalmic drugs with a lag of five minutes between administrations was also taught (see "Dosage and Administration", third paragraph). The difference was thus the addition of timolol. This difference had as the only possible effect a concentration-linked reduction of side effects, as described in document (4) (column 3, lines 26-34). Documents (33) and (34) could not be considered when assessing the presence of a surprising effect, since they were post-published and related to an effect that had not been described in the application as filed. Consequently, the technical problem was the provision of an alternative formulation for the required reduction of ocular hypertension. It was well known that the addition of a further active relying on a different mechanism would have led to the required reduction. Furthermore, it was well known that fixed combinations had advantages for patient compliance. The criteria for selecting a second active for a combination therapy were well established (see documents (44) and (45)). Furthermore, timolol was well known and characterised and had been disclosed in combination with many different actives, including prostaglandin-derived actives (see documents (2) to (6), (10), (20) and (24)). It was thus a normal step in the development of treatments to use the modern bimatoprost also in combinations. Consequently, the subject-matter of the claims of the patent in suit was obvious.

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

Regarding the intervention, the respondent had no objections.

Sufficiency of disclosure

Claim 1 was a second medical use claim. From the example disclosed in the description, it was known that a composition comprising timolol and bimatoprost could be made. The two actives were well known, available and well characterised. The selection of a particular dose would be made according to the factors set out in paragraph [0044] of the patent in suit. In reading the claim with a mind willing to understand, the skilled person would have been led to disregard very high and very low doses in a second medical use claim. Any effects relating to side effects were not claimed and thus should be discussed only in the context of inventive step.

Novelty

Document (10) did not directly and unambiguously disclose a combination of timolol and bimatoprost. Claim 1 gave only a generic disclosure of classes of compounds, the description provided lists of β -adrenergic antagonists and prostaglandins, prostaglandin derivatives or hypotensive lipids.

Inventive step

Many different compounds were known for reducing intraocular pressure. A skilled person would have tried to find a balance between the reduction of intraocular pressure and side effects. The provision of a fixed combination was problematic. Mechanistic considerations greatly influenced any expectation of success. This

could be seen from the passages of document (4) which discussed the mechanism of action of the prostaglandins and described considerations based on this mechanism of action (column 1, line 48 to column 2, line 36). A skilled person would have known from document (7), page 724, left-hand column, first paragraph under the heading "Pharmacology" and Table 1, that bimatoprost acted by a different mechanism than the prostaglandins and their derivatives. In the absence of a reasonable expectation of success of the replacement, the person skilled in the art would have refrained from changing PGF2 α isopropylester or latanoprost to bimatoprost, or, when starting from a mono-therapy, to create an entirely new combination, especially a new fixed combination. The subject-matter of the claims of the patent as granted involved an inventive step.

IX. The final requests of the parties are as follows:

The appellant requested that the decision under appeal be set aside and the patent be revoked in its entirety.

Opponent 3 requested that the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed.

Opponent 2 had no requests in appeal.

Reasons for the Decision

1. The appeal is admissible.
2. *Intervention*

The notice of intervention satisfies the requirements of Article 105 EPC and the Implementing Regulations. This was not disputed by the proprietor. Thus, the intervention was admissible.

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

4. *Sufficiency of disclosure (Article 100(b) EPC)*

Claim 1 is defined as a second medical use claim limited to treating ocular hypertension. Claim 6 is a claim to a composition.

4.1 An example composition was manufactured in the examples section of the patent in suit. In the absence of any evidence showing that the manufacture of further compositions might be problematic, there are no doubts that compositions across the whole scope of the claims can be prepared.

4.2 Furthermore, no doubts were substantiated that the two actives, timolol and cyclopentane N-ethyl heptenamide-5-cis-2-(3 α -hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1 α ,2 β ,3 α ,5 α] (bimatoprost), which are known for their hypotensive activity and have been shown to exert this activity also in combination (see Figure 1), would not display this activity at concentrations other than the tested one. It was acknowledged by the opponents and the respondent that the combined action is close to additive. The effective concentrations of the single actives seem to be well established in the art.

4.3 The attention of the board has been drawn to the broad concentration range for the active agents described in paragraph [0043] of the patent. In the table in paragraph [0043], a very low concentration, 0.00005 wt-%, is taught for the hypotensive lipid component.

The board notes that claim 1 as granted does not define merely any hypotensive lipid component. It specifically defines bimatoprost. The usual unit dose of bimatoprost, which is well known (see document (52)), lies well within the preferred range generally described for hypotensive lipids (see paragraph [0035] of the patent). Also, basic considerations concerning the dosing of hypotensive actives are well known to the skilled person, as acknowledged in the patent in paragraph [0044]. The skilled person, following the teaching of the patent itself and having in mind the common general knowledge, would thus be guided on how to proceed in case of failure of very low doses.

4.4 Therefore, the therapeutic effect underlying the treatment of ocular hypertension, which is a functional technical feature of claim 1, is attained by the claimed composition.

4.5 No additional effects are defined by technical features of the claims under consideration. It is established case law that an objection of insufficiency of disclosure cannot legitimately be based on the consideration that the application, at its effective date, had not made it plausible that a non-claimed technical effect arose, in line with the decision of the Enlarged Board of Appeal G 1/03 (OJ EPA 2004, 413, reasons 2.5.2). There is thus no need for the board to assess whether any additional effects arise or were

made plausible at the filing date of the patent.

4.6 Consequently, the invention as defined in the claims is sufficiently disclosed in the patent and the ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent.

4.7 *Further arguments*

The opponents referred to decision T 967/09, in particular, point 12, which reads:

"Sufficiency of disclosure requires that the teaching of the application (Article 83 EPC) or the patent (Article 100(b) EPC) enables the skilled person to carry out the (whole) subject-matter of a claim without undue burden. The disclosure of a patent application or patent is aimed at the skilled person. It is an accepted principle in patent law that the same skilled person with the same level of skill has to be considered when, for the same invention, the two questions of sufficiency of disclosure and inventive step are being considered (see Case Law of the Boards of Appeal of the EPO, II.C.3.1). It is also the same skilled person that has to be considered when construing the subject-matter of a claim. It accordingly follows that the construction of a particular claim should be identical for the assessment of inventive step and sufficiency of disclosure."

The situation underlying decision T 967/09 is not directly comparable with the present situation, since effects are neither defined in the claims underlying decision T 967/09 nor addressed in the cited passage (see above).

An assessment of whether the same effects have to be considered in the context of sufficiency of disclosure and inventive step is not necessary in the present case.

5. *Novelty (Article 100(a) and Article 54(1) EPC)*

Document (10) defines an ophthalmic formulation for the treatment of ocular hypertension and glaucoma. The formulation comprises a carrier, (a) a carbonic anhydrase inhibitor, (b) a β -adrenergic antagonist and (c) a prostaglandin or prostaglandin derivative or a hypotensive lipid derived from a prostaglandin or prostaglandin derivative (claim 1).

Timolol is explicitly mentioned in several passages. For example, on page 5, line 27, in a passage limiting the topical carbonic anhydrase inhibitor to a group of compounds having the structural formula II, a list of several β -adrenergic antagonists is given, two of which are declared as being preferred. The two which are preferred in this context are betaxolol and timolol. 33 out of 47 examples comprise timolol as the β -adrenergic antagonist. The other examples all comprise metipranolol as the β -adrenergic antagonist. Consequently, there are three β -adrenergic antagonists highlighted in these passages of the description of document (10).

Prostaglandins and prostaglandin derivatives are discussed in various passages of the description, including lists of several possible, explicitly listed, compounds. On page 10, lines 3 to 18, hypotensive lipids are discussed under "PGF 2α lipid analogs". AGN 192024 (bimatoprost) is mentioned.

The opponents argued that the fact that timolol is highlighted twice, once on page 5 of the description and once in the examples as being one of the two example β -adrenergic antagonists, implies a clear preference for timolol. Consequently, a single selection, the choice of bimatoprost as a prostaglandin-related active, suffices to arrive at the subject-matter of claim 1 of the patent in suit.

The board cannot accept this line of argument. It follows clearly from the description of document (10) that β -adrenergic antagonists other than timolol are also preferably used. See, for instance, page 5, line 27, where two β -adrenergic antagonists are preferred, and the examples which explicitly use two β -adrenergic antagonists. The use of timolol is thus a further selection.

Consequently, there is no direct and unambiguous disclosure of a combination of timolol and bimatoprost in the disclosure of document (10).

The subject-matter of claims 1 and 6 of the patent in suit is novel and the ground for opposition under Article 100(a) and Article 54 EPC is therefore not prejudicial for the maintenance of the patent.

6. *Inventive step (Article 100(a) and Article 56 EPC)*

6.1 The patent in suit relates to the provision of a composition for treating ocular hypertension and providing enhanced benefits and/or having reduced side effects (paragraph [0001]). Compositions comprising timolol and bimatoprost allow for the same or better reduction of intraocular pressure while leading to a reduced number and/or reduced severity of side effects

(paragraphs [0024] and [0026]).

6.2 Two separate lines of arguments have been put forward:

The first starting point for the assessment of inventive step relies on disclosures relating to fixed combinations of timolol and a prostaglandin derivative for the treatment of elevated intraocular pressure. Documents (4) and (24) have been identified as the closest prior art documents.

The second starting point is one of a series of documents that employ bimatoprost in essentially a mono-therapy for the reduction of intraocular pressure. Documents (7), (9) and (52) have been identified as promising springboards.

6.3 *Fixed combinations as closest prior art*

6.3.1 Document (4) defines a method for treating ocular hypertension or glaucoma by administration of a composition comprising an adrenergic blocking agent (β -adrenergic antagonist) and a prostaglandin or prostaglandin derivative (claim 1). PGF 2α isopropylester is the only example of a prostaglandin derivative in document (4). Timolol is one of the preferred β -adrenergic antagonists. Compositions comprising PGF 2α isopropylester and timolol are disclosed. It is stated that the combination is advantageous in that the β -adrenergic antagonists act by reducing the secretion of aqueous humour, whereas prostaglandins act by increasing uveoscleral outflow (column 3, lines 18 to 26). By combining these two classes of actives, it is possible to reduce the concentration of each active which results in a significant reduction in the occurrence of

side effects (column 3, lines 26 to 34).

- 6.3.2 Document (24) aims at providing an effective treatment of ocular hypertension by administration of a single-dose (i.e. once daily) of a fixed combination of latanoprost and timolol (title, abstract, paragraph bridging pages 125 and 126, page 127, right column, lines 10 to 5 from the bottom). Similar adverse events for the respective mono-therapies or the non-fixed combination were observed (page 127, right column, second paragraph).
- 6.3.3 The difference between the independent claims of the patent in suit and documents (4) and (24) is the choice of the second active agent. Starting from document (4) PGF2 α isopropylester, starting from document (24) latanoprost is replaced with bimatoprost.
- 6.3.4 The replacement with bimatoprost allegedly leads to a reduction of side effects. However no data showing a direct comparison between compositions according to documents (4) or (24) and a composition according to the claims of the patent in suit was invoked by the respondent in appeal proceedings.
- 6.3.5 As a consequence, the technical problem has to be seen as the provision of an alternative fixed combination for the treatment of ocular hypertension.

In line with points 4.2 and 4.3 above, this problem is considered to be solved.

- 6.3.6 The opponents argued that it was obvious to replace one hypotensive active with another hypotensive active, especially since bimatoprost would have been considered by the skilled person to be a member of the same class

of actives as PGF2 α isopropylester and latanoprost.

Bimatoprost has a molecular structure that is very similar to the structures of prostaglandins, especially to the structures of PGF2 α isopropylester and latanoprost. One difference lies in the replacement of the isopropylester moiety with an ethylamide group in bimatoprost. Bimatoprost further differs from PGF2 α isopropylester by having a phenyl substituent instead of a n-propyl group at the end of the omega chain. A skilled person would be, however, well aware that small differences in structure may lead to major differences in activity. This general knowledge is confirmed by the mechanistic considerations as set out in the following.

Document (7) teaches that a considerable part of the activity of bimatoprost is probably due to an increase of uveoscleral humour outflow (page 723, right column, last paragraph). Document (7) then discloses that bimatoprost has no affinity to prostaglandin receptors (page 724, "Pharmacology", first paragraph, Table 1). Consequently, it cannot act, like PGF2 α isopropylester and latanoprost, via binding to the prostaglandin receptor. Document (7) thus provides evidence that at the effective date of the patent in suit, a skilled person would not have considered bimatoprost to be a functionally equivalent derivative of prostaglandins.

Document (4) discusses in detail the mechanistic considerations that led to the selection of certain prostaglandin derivatives as suitable hypotensive actives for combined use with β -adrenergic antagonists. Document (4) starts off by stating that prostaglandins reduce intraocular pressure by increasing uveoscleral outflow (column 1, lines 48 to 52). It is then

explained that uveoscleral outflow is caused by the relaxation of the muscle part of the ciliary body, i.e. the aqueous humour passes through extracellular space between muscle fibres (column 2, lines 3 to 13). The mechanistic considerations are continued in a discussion on how prostaglandins effect this relaxation. Only one of the two possible mechanisms underlying this increase in uveoscleral outflow, on a molecular basis, is considered to be acceptable for an active that is to be combined with β -adrenergic antagonists. This mechanism must be a molecular mechanism that is not based on the release of catecholamines but on an interaction with prostaglandin receptors (column 2, lines 14 to 36). Therefore, document (4) clearly teaches that specifically prostaglandins and derivatives of them that interact with the prostaglandin receptor are suitable for combining with β -adrenergic antagonists. The combination of β -adrenergic antagonists with compounds that rely on other mechanisms of action is stated to be potentially counterproductive. It is thus clear from document (4) that for the provision of effective fixed combinations mechanistic considerations on the molecular level, i.e. going beyond the inflow/outflow scheme, are decisive.

The skilled person would thus have been well aware that mechanisms on a molecular basis were decisive when deciding on the combination of two hypotensive compounds.

When assessing issues relating to the mechanisms of action, post-published documents (such as documents (40) to (42)) are disregarded by the board, since they cannot elucidate the knowledge of the skilled person

before the effective date of the patent in suit.

The opponents emphasised on the disclosure of document (9). They explained that document (9) taught that bimatoprost was a new advantageous development in the line of prostaglandin derivatives that would consequently have been used by the skilled person as a replacement for the prostaglandin derivatives of documents (4) or (24). In fact, document (9) discloses a group of compounds that are potent ocular hypotensives and particularly suitable for the treatment of glaucoma (column 1, second paragraph). The compounds are presented as an advantageous development in view of the related art, e.g prostaglandin derivatives, such as PGF₂α isopropylester and latanoprost (column 2, lines 33 to 53). The inventive compounds of document (9) replace the carboxylic acid group, presumably of the related prostaglandin, with a non-acidic substituent. Good potency and lower ocular surface hyperemia than the parent compounds were found (column 3, lines 9 to 19). Several specific compounds, some esters and some amides, are disclosed and some of them are synthesised and used in examples. Bimatoprost, which is neither synthesised nor used in the examples, is listed by its chemical formula as compound (9) in column 7 and defined in a list of specific compounds in claim 10. Document (9) is, however, completely silent on the mechanism of action of its new class of compounds.

6.3.7 The provision of a fixed combination in the specific case of treating ocular hypertension is not per se trivial. The skilled person would be aware that careful considerations concerning the choice of the active agents have to be made to avoid effects that may be counterproductive in view of the condition to be

treated. Consequently, the skilled person, in the specific case of the treating ocular hypertension, would not simply combine any active agent with any other active agent. When trying to provide an alternative fixed combination the skilled person would take particular care to replace one active only with another active known to act by exactly the same mechanism on a molecular basis. Since there is evidence that PGF2 α isopropylester/latanoprost act via different receptors than bimatoprost, the skilled person would not have replaced PGF2 α isopropylester or latanoprost with bimatoprost when aiming at the provision of an alternative fixed combination.

- 6.3.8 Starting from either document (4) or document (24) the claimed subject-matter is a non-obvious alternative.
- 6.4 *Mono-therapies and non-fixed combinations as the closest prior art*
- 6.4.1 Document (7) focuses entirely on bimatoprost. The title indicates that the author considers bimatoprost to belong to a class of actives which differs from known classes, it reads: "Bimatoprost: a member of a new class of agents, the prostamides, for glaucoma management". Document (7) teaches that bimatoprost influences humour outflow by increasing tonographic outflow facility by approximately 35% and by increasing pressure-independent outflow, probably corresponding to uveoscleral outflow, by approximately 50% (page 723, right-hand column, last paragraph). Under the heading "Pharmacology", it is indicated that bimatoprost is not a prodrug, i.e. it acts directly as an amide. It has also no affinity for the prostaglandin receptor (page 724, left-hand column, first paragraph and Table 1).

Document (9) concerns a new class of compounds suitable for the treatment of glaucoma (column 1, second paragraph). The compounds are presented as an advantageous development in view of the related art, e.g. prostaglandin derivatives, such as PGF₂α isopropylester and latanoprost (column 2, lines 33 to 53). The inventive compounds of document (9) contain a replacement of the carboxylic acid group, presumably of the related prostaglandin, with a non-acidic substituent. Good potency and lower ocular surface hyperemia than the parent compounds were found (column 3, lines 9 to 19). Several specific compounds are disclosed and some of them are synthesised and used in examples. Bimatoprost, which is neither synthesised nor used in the examples, is listed by its chemical formula as compound (9) in column 7 and defined in a list of specific compounds in claim 10. In document (9), column 11, lines 48/49, a combination with "other of the known vasodilator drugs" is taught. This passage has to be read in combination with the preceding paragraph dealing with the treatment of various pathophysiological diseases relating to heart conditions. This preceding paragraph is the only paragraph in document (9) that mentions an effect of vasodilation. This passage does thus not concern the treatment of ocular hypertension.

Document (52) provides information on the medicament LumiganTM, a 0.03% bimatoprost ophthalmic solution. Bimatoprost is identified as being a prostamide, which is a synthetic structural analogue of prostaglandin. The ocular hypotensive activity is achieved by increasing outflow of aqueous humour through both the trabecular meshwork and uveoscleral routes (page 1, "Mechanism of Action"). As a major adverse reaction, conjunctival hyperemia is identified (page 5, "Adverse

Reactions", first paragraph). In contrast to documents (7) and (9), document (52) mentions in very general terms the use of a further active agent for the treatment of ocular hypertension. Under the heading "Dosage and Administration" on page 6, it is stated in the third paragraph that LumiganTM may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, when keeping administration at least five minutes apart. A similar statement can be found on page 4, paragraph 8. Despite the fact that no suggestion as to the identity of the other topical ophthalmic drug is made, the disclosure in document (52), which in view of the considerations above is closer to the claimed subject-matter than the disclosure of documents (7) or (9), constitutes the closest prior art for the problem-solution approach starting from non-fixed combinations.

- 6.4.2 The difference between the independent claims of the patent in suit and the disclosure of document (52) is the addition of a further compound capable of reducing intraocular pressure in form of timolol in a fixed combination.
- 6.4.3 The technical problem may thus be seen as the provision of a safe and effective composition leading to a further reduction, in compared with the reduction achieved by the sole administration of bimatoprost, of intraocular pressure in the treatment of ocular hypertension.
- 6.4.4 There is no doubt that the addition of timolol leads to a further reduction of intraocular pressure compared with the administration of bimatoprost alone. Reference is made to the data of the patent in suit, e.g. as

presented in Figure 1.

- 6.4.5 Information representing the common general knowledge on the treatment of ocular hypertension and in particular on the provision of drug combinations for such a treatment can be found in documents (44) to (46).

Document (44) relates to antiglaucoma drugs. It states that a myriad of pharmacologic agents is available to decrease intraocular pressure through distinctly different mechanisms. Because of their unique mechanisms of action, these drugs may be used both alone and in combination (page 183, left-hand column, second paragraph).

Document (45) contains a section dealing explicitly with the "Combination of Antiglaucoma Drugs". The combining of drugs from different classes involving different modes of action can be employed when the application of one drug does not lower the intraocular pressure sufficiently (page 245, left column, third paragraph). Several combinations are discussed, including PGF₂α isopropylester with timolol for patients that responded poorly to timolol (page 245, right-hand column, fifth paragraph). The next paragraph (page 245, right-hand column, sixth paragraph) relates to "proper" combinations and teaches that they lead to an enhanced reduction in intraocular pressure and cause longer-lasting effects. No details are mentioned.

Document (46), cited in the written procedure, confirms that prostaglandins lower the intraocular pressure in patients whose pressures are inadequately controlled by timolol alone (page 96, left-hand column, middle

paragraph).

However, it is not clear whether any of documents (44) to (46) refers to fixed combinations. The provision of a fixed combination requires considerations on at least two levels. Firstly, the skilled person would have to choose two active agents that are suitable for combination. In the present case of hypotensive active agents the selection criteria would focus mainly on mechanisms of action and side effects. Furthermore, for a fixed combination, the possibility of interaction/reaction/influence of respective stabilities of the two actives when they are provided in the same composition would also play a role. A second aspect concerns the matrix of the fixed composition. It must ascertain a suitable shelf life and provide safe and effective delivery of the combined agents. Further issues may also arise, e.g. relating to dosage regimens. Guidance would thus be needed as to which two actives are promising from both a therapeutic and a formulation related point of view.

The opponents selected a document essentially relating to a mono-therapy by bimatoprost or vaguely proposing a further active agent to be administered at a time interval of at least 5 minutes as the closest prior art. It is questionable whether a skilled person starting from this point would have consulted documents relating to combinations not including bimatoprost for guidance. Documents not including bimatoprost provide neither guidance as to the suitability of the combination for achieving the therapeutic effect nor information on formulation related issues.

Document (52) itself does not give any clear guidance concerning concrete combinations. It provides

information on the concomitant administration of two hypotensive actives, but without indicating which second hypotensive active would be suitable.

Document (7) is silent on combinations. Document (9) discusses combinations for a different therapeutic purpose. There is no information on fixed combinations including bimatoprost and further hypotensive actives on file. Thus, there is no guidance for the skilled person on which hypotensive actives would be advantageous in combination, especially in a fixed combination, with bimatoprost.

Consequently, the question to be answered is whether the skilled person would simply use any of the known hypotensive actives which is acting by a physiological mechanism other than increasing aqueous humour outflow in combination with bimatoprost.

The opponents argued that timolol was "the" hypotensive active used for reducing intraocular pressure and that timolol was well established in combination treatments. Specific combinations were disclosed in documents (4) and (24) (see above) and in documents (2) (timolol + carbonic anhydrase inhibitor), (3) (timolol + brinzolamide), (5) (timolol + 15-deoxy-prostaglandin compound), (6) (timolol + (13,14-dihydro-15-ketoprostaglandin compound), (10) (see above) and (20) (timolol + glutamate antagonist). The skilled person would thus automatically consider timolol when aiming at providing a fixed combination.

However, the closest prior art document discloses the use of bimatoprost essentially for mono-therapy and does not mention further specific hypotensive actives. Starting from such a disclosure involves an *ex post facto* analysis to rely on the teaching of documents

referring to the second claimed active in combination with further actives, which are irrelevant in the context of the patent in suit.

Furthermore, in analogy to the considerations under point 6.3.6 above, the skilled person would have reservations when combining bimatoprost with a β -adrenergic antagonist such as timolol. The skilled person would have in mind the caveat from document (4) that, depending on the mechanism underlying the uveoscleral outflow, a combination with a β -adrenergic antagonist could be counterproductive.

In the absence of a clear mechanistic explanation, on a molecular basis, of the activity of bimatoprost, the skilled person would not have combined bimatoprost with timolol when aiming at providing a safe and effective fixed combination leading to a further reduction of intraocular pressure in the treatment of ocular hypertension. Therefore, the provision of a combination of bimatoprost and timolol for the treatment of ocular hypertension involves an inventive step.

6.4.6 Having thus come to the conclusion that the subject-matter of claims 1 and 6 involves an inventive step when considering the technical problem defined in point 6.4.3 above and also when considering the technical problem defined in point 6.3.5 above, it is not necessary to establish whether a technical problem involving the reduction of the side effect of conjunctival hyperemia may be formulated.

6.4.7 *Further arguments*

(a) The opponents further argued that the skilled person would have combined any prostaglandin

derivative with timolol and have expected an at least additive effect in the decrease of intraocular pressure. The subject-matter of the patent in suit would thus be the result of the normal next step in the development of prostaglandin derivative based products.

The board cannot concur with this argument, since the skilled person would not have considered bimatoprost to be a member of the prostaglandin class at the effective date of the patent in suit.

- (b) The opponents have further argued that it was a well-known fact that fixed combinations improved patient compliance. The skilled person, following the teaching in document (52) (page 6, "Dosage and Administration") to concomitantly administer other topical ophthalmic drug products to lower intraocular pressure, would have opted for a fixed combination knowing from its general common knowledge that timolol was the most commonly used agent to be combined with prostaglandin derivatives.

It has been established above that the skilled person would not have considered bimatoprost to belong to the class of hypotensive prostaglandin derivatives. The provision of a fixed combination having patient compliance in mind has to be seen as a further step, once the two actives to be combined have been decided on. Consequently, the board cannot accept the opponents' argument.

- (c) It was also argued that a skilled person would have been aware of the teaching of document (4) that the combination of two actives would allow for the same

hypotensive effect while leading, due to the administration of a reduced amount of each of these two actives, to less severe side effects.

Consequently, when starting from a mono-therapy by a compound having severe side effects, the skilled person would have simply added a second active, knowing that the reduction of the concentration of both of the two now present actives would have led to a reduction of side effects.

Having come to the conclusion that in the case of the provision of fixed combinations for the treatment of ocular hypertension the skilled person would not have simply combined any two actives, the question of concentrations and side effects does not arise for the board in the present case.

- 6.5 The subject-matter of claims 1 and 6 of the patent in suit involves an inventive step and, therefore, the ground for opposition under Article 100(a) and Article 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated