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**Datasheet for the decision
of 17 April 2012**

Case Number: T 1064/08 - 3.3.02

Application Number: 03726234.2

Publication Number: 1496912

IPC: A61K 31/535, A61K 31/498,
A61P 27/06

Language of the proceedings: EN

Title of invention:
Combination of brimonidine and timolol for topical ophthalmic
use

Applicant:
ALLERGAN, INC.

Headword:
Combination of brimonidine and timolol/ALLERGAN

Relevant legal provisions:
EPC Art. 56

Keyword:
"New main request novel and inventive"

Decisions cited:
-

Catchword:
-



Case Number: T 1064/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 17 April 2012

Appellant:
(Applicant)

ALLERGAN, INC.
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Representative:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 11 December 2007
refusing European patent application
No. 03726234.2 pursuant to Article 97(1)
EPC 1973.

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
R. Cramer

Summary of Facts and Submissions

I. European patent application No.03726234.2, based on international application No. WO 03/088973, was filed with 14 claims.

II. The following documents *inter alia* have been cited in the examination and appeal proceedings:

D1 N. Yürsel, *Ophthalmologica*, 213: 228-233, 1999

D2 L. Larsson, *Arch. Ophthalmol.*, vol. 119, 492-494, April 2001

D3 R. Wang et al., *Journal of Glaucoma*, vol. 9, 458-462, 2000

D4 A.B. Hommer, *Investigative Ophthalmology & Visual Science*, vol. 42, No. 4, supp., 15 March 2001, page 554 (2974-B116)

D5 W.C. Stewart, *Current Opinion in Ophthalmology*, vol. 10, 99-108, 1999

D6 P.F.J. Hoyng, *Drugs*, vol. 59, No. 3, 411-434

D7 J.S. Schuman, *Survey of Ophthalmology*, vol. 41, No. 1, S27-S37, 1996

D8 data sheet for timolol

D9 data sheet for brimonidine

D10 excerpt from the double-masked, randomized, clinical study underlying the application in suit (filed with the appellant's letter of 16 April 2008)

D11 J. Connor et al. BMJ, vol. 324, 1-5, 11 May 2002

D12 Final Study Report, Allergan Study Number: A342-119-7831, filed with appellant's letter of 14 March 2012

III. The present appeal lies from a decision of the examining division refusing the application (Article 97(1) EPC 1973).

IV. The examining division's decision was based on the main (sole) request filed with letter of 27 December 2004. The examining division considered that the claimed ophthalmic composition comprising timolol and brimonidine in a pharmaceutically acceptable carrier lacked an inventive step (Article 56 EPC). The examining division defined two documents, namely D1 and D2 as closest prior art. The examining division stated that the sequential administration of brimonidine and timolol was known from documents D1 and D2.

The examining division's decision also mentioned that the applicant's definition of the problem to be solved was how to provide a medication with fewer side effects than the medications in documents D1 and D2 and that the proposed solution was the provision of a "combined composition comprising both brimonidine and timolol, which allows the concomitant administration of the two components".

The examining division's decision denied the importance of reducing the systemic side effects (decreased heart rate/decreased blood pressure) since the systemic side effects caused by the sequential application of the two active ingredients were "minimal". Moreover, the examining division stated that inventive step could not be acknowledged in the absence of a clear comparison with the closest prior art showing the actual data results.

- V. The applicant (appellant) filed an appeal against said decision and filed grounds of appeal. With its grounds of appeal it filed documents D8 to D10.

- VI. The appellant filed a letter dated 19 August 2011 in which it reproduced additional comparative data from clinical studies. It also filed document D11 as an annex thereto.

- VII. A communication expressing the preliminary opinion of the board was sent pursuant to Article 15(1) RPBA as an annex to the summons for oral proceedings to be held on 17 April 2012.

- VIII. The appellant filed a reply dated 14 March 2012 to the board's communication. It filed therewith a new main request and document D12. The appellant requested that the oral proceedings scheduled for 17 April 2012 be cancelled should the board find the claims of the new main request allowable.

Claim 1 of the main request reads as follows:

"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".

IX. The appellant was informed that the oral proceedings had been cancelled.

X. The appellant's submissions may be summarised as follows:

The main request contained only one independent claim, so that the requirements of Rule 43(2) EPC were complied with. Claim 1 was drafted as a purpose-limited product claim within the meaning of Article 54(5) EPC.

The active ingredients were specified as brimonidine tartrate and timolol maleate in accordance with the application as filed, in particular page 2.

Contrary to the examining division's opinion, reducing the side effect profile of a given drug is an integral and most important part of any pharmaceutical development. Achieving such a reduction is a substantial contribution to the art. Side effects relating to heart rate and blood pressure are material and relevant for timolol and brimonidine and are listed in the product data sheets. The closest prior art reference was document D1, which discloses that a sequential use of timolol and brimonidine is beneficial

on the elevated IOP (intraocular pressure) over the sole use of either component in isolation. However, D1 notes that the sequential use of timolol and brimonidine leads to significant side effects (decrease in mean systolic blood pressure, decrease in diastolic blood pressure and reduction of mean pulse rate).

The appellant further submitted that the present "invention", which relates to the simultaneous administration of the two active ingredients timolol and brimonidine in one single pharmaceutical composition, provided an improvement of side effects such as somnolence and dry mouth over the sequential use without having a stronger impact on the heart rate and the blood pressure than timolol or brimonidine in isolation (document D10).

Moreover, the appellant referred in its letter dated 19 August 2011 to data results obtained in clinical studies for the request of market approval in the US of a combination composition of brimonidine tartrate and timolol maleate (0.2%/ 0.5%). In these studies the simultaneous administration of the combination of brimonidine and timolol in one single pharmaceutical composition showed fewer side effects in relation to effects on the nervous system (in particular somnolence) and oral dryness than the sequential administration of the active ingredients. The significance of driver sleepiness was shown in document D11. Thus, the combination composition for which the use was claimed had *inter alia* a positive benefit to risk ratio providing both added IOP lowering efficacy and important safety benefits over the sequential use of brimonidine and timolol. The appellant also referred to

the clinical studies in document D12 in order to show that no significant difference in any safety parameters (e.g. side effects in relation to somnolence and oral dryness) was shown in the administration twice daily (BID) and thrice daily (TID) of brimonidine. Thus, it was immaterial for the comparison in relation to the occurrence of the side effects whether brimonidine was given BID or TID. Thus, the comparative data provided in the letter of 19 August 2011 showed that the simultaneous administration of the two active ingredients in one single pharmaceutical composition solved the technical problem of reduction of side effects in a plausible manner. The proposed solution was not obvious in the light of the cited prior art.

- XI. The appellant requested that the decision under appeal be set aside and the case remitted to the first instance with an order to grant the application on the basis of the main request filed with the letter of 14 March 2012.

Reasons for the Decision

1. *Admissibility*
 - 1.1 The appeal is admissible.
 - 1.2 The new main request filed with the letter of 14 March 2012 is admissible since it represents a clear and direct response to the board's communication sent pursuant to Article 15(1) RPBA and it is simple to handle.

2. *Main request*

2.1 The new main request contains only one independent claim, which is a purpose-related product claim (within the meaning of Article 54(5) EPC 2000) relating to a pharmaceutical composition simultaneously containing brimonidine tartrate and timolol maleate for use in a method of treatment of glaucoma or ocular hypertension. Thus, claim 1 addresses the simultaneous administration of the two active ingredients in one single pharmaceutical composition for the treatment of glaucoma and ocular hypertension.

The main request meets the requirements of Articles 123(2) (see *inter alia* pages 1 to 3 of the application as filed) and 84 EPC.

2.2 Moreover, the subject-matter claimed in claim 1 meets the requirements of novelty (Article 54 EPC) since none of the cited documents discloses a pharmaceutical composition simultaneously containing both active ingredients. In fact, none of the cited documents discloses the simultaneous administration of both ingredients. Documents D1 and D2 disclose the sequential administration of the active ingredients with a five-minute interval using two separate pharmaceutical compositions.

2.3 Document D1, which discloses the treatment of glaucoma or intraocular hypertension with the sequential administration of the drugs brimonidine (0.2%) and timolol in two separate pharmaceutical compositions or, alternatively, document D2, which discloses the treatment of elevated intraocular pressure with the

sequential administration of brimonidine tartrate (0.2%) and timolol maleate (0.5%) in two separate pharmaceutical compositions, represents the closest prior art.

The problem to be solved lies in the provision of a medication for the treatment of glaucoma or ocular hypertension that has fewer side effects, in particular in relation to somnolence and oral dryness.

The reduction of side effects by means of administration of the combination of active ingredients in one single composition was explicitly mentioned in the application as filed, page 1. Moreover, reduction of side effects (*inter alia* somnolence and dry mouth) was investigated in the examples (see page 13). Additionally, the reduction of side effects is not an arbitrary co-lateral effect but a significant part of a successful medium- and long-term therapy.

The technical data submitted during appeal proceedings (in particular with the appellant's letter dated 19 August 2011), which are extracted from the clinical studies and concern the comparison between the simultaneous administration in one single pharmaceutical composition of both active ingredients, and the sequential administration of the separate ingredients show that the problem has been plausibly solved. Document D12 further illustrates that the same level of side effects is attained by the BID and TID administration of brimonidine (see appellant's letter dated 14 March 2012). Therefore, the comparison submitted with the letter of 19 August 2011 concerns an acceptable comparison of the simultaneous *versus* the

sequential administration of the two active ingredients, which shows a significant decrease in side effects (somnolence, dry mouth) vis-à-vis the closest prior art.

The solution to the problem lies in the simultaneous administration of the two active ingredients in one single pharmaceutical composition.

None of the cited documents gives any hint as to how to attain a reduction in side effects (in particular somnolence and dry mouth).

In view of the above analysis, the subject-matter of claim 1 of the main request meets the requirements of Article 56 EPC. Claims 2 to 4 are dependent claims on claim 1 and, thus, the conclusion achieved for claim 1 applies for analogous reasons.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the set of claims of the main request filed with the letter of 14 March 2012 and a description to be adapted.

The Registrar:

The Chairman:

N. Maslin

U. Oswald