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**Datasheet for the decision
of 10 May 2012**

Case Number: T 2402/10 - 3.3.10

Application Number: 02009255.7

Publication Number: 1225168

IPC: C07C 405/00, A61K 31/557,
A61P 27/02

Language of the proceedings: EN

Title of invention:

Prostaglandin derivatives for the treatment of glaucoma or
ocular hypertension

Patentee:

Pfizer Health AB

Opponents:

Breath Limited
Apotex España SL
ALAPIS S.A.

Headword:

Prostaglandin derivatives / Pfizer

Relevant legal provisions:

EPC Art. 54, 56, 76(1), 111(1), 123(2)

Keyword:

"Amendments (allowable) - no added matter"
"Novelty (yes)"
"Inventive step (yes) - solution not obvious"
"Double patenting (no) - not the same subject-matter"

Decisions cited:

G 0001/05, G 0001/06, T 0548/91, T 0643/96, T 0307/03,
T 0469/03, T 0936/04, T 0877/06, T 1708/06, T 1391/07

Catchword:

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Case Number: T 2402/10 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 10 May 2012

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted 15 November 2010
revoking European patent No. 1225168 pursuant
to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: P. Gryczka
Members: J.-C. Schmid
F. Blumer

Summary of Facts and Submissions

- I. The Appellant (Proprietor of the patent) lodged an appeal against the decision of the Opposition Division revoking European patent No. 1 225 168.
- II. Notices of opposition were filed against the granted patent by the Respondents I, II and III (opponents 1, 2 and 5 respectively) and by former opponents 3 and 4 requesting revocation of the patent-in-suit in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC), of insufficient disclosure (Article 100(b)), and of extending the subject-matter of the patent in suit beyond the content of the application as filed (Article 100(c) EPC). *Inter alia* the following documents were cited.
- (1) Granström "Metabolism of 17-phenyl-18,19,20-trinor-prostaglandin F_{2α} in the cynomolgus monkey and the human female", Prostaglandins, vol. 9, 1975, pages 19 to 45,
- (7) The Association for Research in Vision and Ophthalmology; Annual Spring Meeting; Sarasota, Florida, USA, May 1-6, 1988: Investigative Ophthalmology and Visual Science, Vol. 29, supplement, Abstracts, page 325, and
- (10) Bito "Comparison of the Ocular Hypotensive Efficacy of Eicosanoids and Related Compounds", Exp. Eye Research, 1984, vol. 38, pages 181-194.

According to the opponents, claim 1 as granted lacked novelty with respect to document (1). The subject-

matter of claim 1 was obvious starting from document (7) as the closest prior art. Document (7) taught the IOP lowering effect of $\text{PGF}_{2\alpha}$ and analogues such as 13,14-dihydro- $\text{PGF}_{2\alpha}$ and 17-phenyl-18,19,20-trinor $\text{PGF}_{2\alpha}$. There was no evidence in the patent-in-suit that the technical problem of providing pharmaceutical efficacy in the treatment of glaucoma and ocular hypertension with less irritation and vasodilatation was solved by using the $\text{PGF}_{2\alpha}$ derivatives of granted claim 1. Even, the patent-in-suit stated that the 13,14-dihydro-17-phenyl-18,19,20-trinor $\text{PGF}_{2\alpha}$ isopropyl ester had poor intraocular pressure (IOP) reducing effects in cats. The objective technical problem had to be reformulated as providing further $\text{PGF}_{2\alpha}$ derivatives, while accepting poor IOP lowering efficacy, and accepting the toxicity of the compounds. The skilled man would have combined the structural characteristics of the 17-phenyl-18,19,20-trinor $\text{PGF}_{2\alpha}$ with the single bond between position 13 and 14 of the 13,14-dihydro $\text{PGF}_{2\alpha}$, and thus would have arrived at the compounds of claim 1 without the exercise of inventive step. Furthermore, the fact that the derivatives of claim 1 were esters could not support an inventive step since document (10) already disclosed esters of prostaglandin derivatives.

III. The Opposition Division held that claim 1 as granted did not meet the requirements of Article 76 (1) EPC and rejected the then pending auxiliary request 2 under Rule 80 EPC. Furthermore the Opposition Division found that claim 1 of the then pending auxiliary requests 7, 10 and 11 did not meet the requirements of Article 76 (1) and 123(2) EPC.

With respect to auxiliary request 7 the Opposition Division found that the requirements of Article 84 EPC were satisfied. However, the amount of the dose and the volume of the composition indicated in the amended claim 1 had no support in the application as filed, since the section on page 8, lines 20 and 21 referred to by the Appellant related to "a dose of about 0.1-30 μ in about 10 to 50 μ of the composition" without indicating the units. The application as filed on page 8, line 24 furthermore reported concentrations of the active compound in the composition of 30 μg to 300 $\mu\text{g}/\text{ml}$, thus casting a doubt on the interpretation of the " μ " symbol. Furthermore the unit could be either a weight or a volume unit. Specifying the amounts of the dose and composition in micrograms and microlitres constituted subject-matter extending beyond the content of the application as filed. The Opposition Division therefore came to the conclusion that claim 1 of auxiliary request 7 did not meet the requirement of Article 123(2) EPC.

There was no other pending auxiliary request in the decision under appeal since the other auxiliary requests were withdrawn. The patent was thus revoked.

- IV. In a communication dated 12 December 2011 pursuant to Article 15(1) RPBA, the Board informed the Parties that it may consider not remit the case to the first instance. The Parties were asked to be prepared to discuss all issues during the oral proceedings before the Board, i.e. *inter alia* also the issue of novelty and inventive step.

- V. With letters dated 21 March 2012 and 8 May 2012, opponent 3 and opponent 4 withdrew their opposition. They are no longer Parties to these opposition/appeal proceedings.
- VI. At the oral proceedings before the Board, held on 10 Mai 2012, the Appellant defended the maintenance of the patent in suit in amended form on the basis of a main and an auxiliary request, both filed with the letter of 9 March 2012. The single claim of the main request is identical to claim 1 of the auxiliary request 7 considered by the Opposition Division in the decision under appeal.

Claim 1 of the main request read as follows:

"1. The use of an effective intraocular pressure reducing amount of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α -isopropyl ester and an ophthalmologically compatible carrier, for the preparation of an ophthalmological composition for the topical treatment of glaucoma or ocular hypertension in a human being, the effective amount comprising a dose of 0.1-30 micrograms of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α -isopropyl ester in 10-50 microlitres of the composition."

- VII. According to the Appellant claim 1 of the main request was supported by the section bridging page 7 and 8 of the application as filed, page 8, line 16 to 22 and page 7, line 33 in combination with the disclosure of the 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α -isopropyl ester, for instance on page 6, line 21 (compound (9)).

It was immediately evident that nothing else than 0.1-30 micrograms and 10-50 microlitres was intended to be described on page 8, lines 21 and 22 which specified erroneously only μ as unit. The determination of the correct units was instantly recognizable from the second full paragraph of page 7 disclosing a dose of 0.1 to 30 micrograms of the active substance per application, and that preferably in one drop of the composition corresponding to about 30 microlitres. This conclusion was reinforced by the range of from 30 μg to 300 $\mu\text{g}/\text{ml}$ recited on page 8, line 26 which fell squarely within the central part of the range of 0.1 to 30 micrograms in 10-50 microlitres of the composition. This conclusion was not altered by the fact that, although being preferably saline solutions, the topical composition could be in the form of an ointment according to page 8, line 7 of the application as filed, since amounts of ointments could also be measured by volume.

Claim 1 related to the use of a composition containing 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF 2α -isopropyl ester. This compound was not disclosed in any of the cited prior art, in particular not in document (1). The claimed subject-matter was therefore clearly novel over the cited prior art.

The closest prior art to the invention was document (7). This document *inter alia* disclosed that 17-phenyl-18,19,20-trinor-PGF 2α reduced the intraocular pressure. The technical problem underlying the invention was the provision of a further prostaglandin analogue having the ability to reduce intraocular pressure and treat

glaucoma or ocular hypertension without exhibiting undesirable side effects, in particular ocular irritation and hyperaemia.

The solution was the provision of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF₂α-isopropyl ester (latanoprost) which was characterized by the presence of a single bond between positions 13 and 14 and by an isopropyl ester moiety. Tables V and VI of the patent-in-suit revealed that latanoprost had an intraocular pressure reducing effect while tables III and IV showed the absence of ocular irritation and hyperemia. Document (7) was totally silent about the side effects of the PGF₂α derivatives and hence did not suggest any solution to the technical problem underlying the invention. Furthermore, there was no incentive in this document to make structural modifications in the PGF₂α derivatives in order to provide further active derivatives. The subject-matter of claim 1 of the main request involved thus an inventive step. Double patenting was not a ground for opposition and thus should not be considered in opposition proceedings. Furthermore the patent derived from the grant parent application, i.e. EP-A-364 417, contained no claim reciting the essential feature relating to the concentration of latanoprost in the composition, and thus did not claim the same invention as the patent-in-suit. Hence the required condition for double patenting did not occur in the present case.

VIII. According to Respondent I the passage of page 8, lines 16 to 22 did not provide an adequate basis for the introduction of the words "micrograms" and "microlitres" in claim 1. Each occurrence of the symbol

"µ" could equally be interpreted as "µl" or "µg", giving rise to different options for a possible correction. Moreover, according to page 8, line 7 of the application as filed, the composition could be in the form of an ointment, thus rendering plausible that the amount of the composition was intended to be expressed as a weight. Furthermore, the passage of page 8, lines 16 to 22 relating to ophthalmological compositions for topical treatment of ocular glaucoma or ocular hypertention was not disclosed in combination with the specific 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF₂α-isopropyl ester. The requirement of Article 123(2) EPC was therefore not satisfied for claim 1 of the main request.

Even if double patenting was not a ground of opposition, according to decision T 936/04 (not published in OJ EPO) it was within the discretion of the instances of the EPO to raise this objection in opposition/appeal proceedings. Claim 14 of EP0364417B9, which was a patent issued from the grant parent application was a so-called "Swiss type" claim concerning the application of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF₂α-isopropyl ester in the treatment of glaucoma or ocular hypertension. Claim 1 of the main request differed from claim 14 of EP0364417B9 only in that the treatment was "in a human being" and the dosage regime was specified. These features were implicit and did not substantially distinguish claim 1 of the main request from the claims of EP0364417B9. In any case, since claim 1 in suit was covered by the claims of EP0364417B9 and thus contravened the principle of prohibition of double patenting for reasons similar to those discussed in the headnote of decision T 307/03 (OJ EPO 2009,422).

Respondent I made no submission in these appeal proceedings with respect to the issues of clarity, insufficiency of disclosure, novelty and inventive step.

- IX. Respondents II and III made no submissions at all in these appeal proceedings, nor did they file any requests.
- X. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with letter dated 9 March 2012, or, subsidiarily, on the basis of the first auxiliary request also filed with the letter dated 9 March 2012.

Respondent I requested that the appeal be dismissed.

- XI. At the end of the oral proceedings held in the absence of Respondents II and III, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.
2. *Procedural matter*

The Appellant requested the Board of Appeal to exercise its discretion in accordance with Article 111(1) EPC and to render a decision on all grounds of opposition raised by the Opponents although the issues of novelty and inventive step were not dealt with by the

Opposition Division in the decision under appeal. None of the Respondents objected to this request. The Board furthermore notes that all Parties had requested acceleration of the opposition proceedings (see the Respondents' letters dated 22 October 2009, 5 October 2009 and 6 November 2009, respectively).

Taking particular account of the fact that all parties wish the opposition proceedings to be concluded without further delay, the Board has chosen to exercise its discretion under Article 111(1) EPC to examine on all opposition grounds raised by the opponents.

Main request

3. Amendments (*Articles 76(1) and 123(2) and (3) EPC*)

3.1 Claim 1 is based on the passage bridging page 7 and 8 of the application as filed in combination with page 8, lines 16 to 22 read with the disclosure of the prostaglandin derivative disclosed on page 6, line 21 (compound 9), and further limited to the treatment of human beings according to page 7, line 33.

The section of page 8, lines 16 to 22 of the application as filed, which relates to ophthalmological compositions for topical treatment of glaucoma or ocular hypertension obviously contains a clerical error in that only the symbol " μ " is indicated for the unit of the dose of the prostaglandin derivative and the dose of the composition. This section reads "a dose of about 0.1-30 μ in about 10-50 μ of the composition". However, throughout the application as filed, the amount of the prostaglandin derivative is always specified by its mass while that of the composition by

its volume. More particularly, the preceding section on page 7, line 22 to 34 relating to the method for treating glaucoma or ocular hypertension discloses that the composition to be contacted with the eye contains 0.1-30 µg of the derivative and that the treatment may advantageously be carried out in a that one drop of the composition corresponding to about 30 µl is administered to the patient's eye. Hence, it appears immediately that nothing else than a dose of about 0.1-30 µg of the derivative in about 10-50 µl of the composition was intended to be specified in the following section relating to the composition for that use. This finding is also in line with the experiments, where the concentration of the prostaglandin in the ophthalmological composition is always given in weight of active compound per volume of the composition (see page 8, line 24 to 28).

- 3.2 In the decision under appeal, the Opposition Division indicated that the paragraph of page 8, starting from line 24 cast a doubt on the interpretation of both "µ" symbols in that it could not be decided whether they should really mean "micro" or whether "milli" was intended.

However, it clear that "milli" could not be intended, otherwise the passage page 8, lines 16 to 22 would have been inconsistent with the remainder disclosure the application as filed, in particular with the section of page 8, starting from line 24. In addition the symbol "µ" designates "micro" and not "milli" which is symbolised by "m".

3.3 The Respondent objected that there was an uncertainty for the unit itself, i.e. it could be either a mass or a volume unit, all the more because the ophthalmological composition encompassed ointments, which were rather solids than liquids.

This argument does not convince the Board since the passage of page 8 is not specifically directed to ointments. Moreover ointments can also be quantified by their volume. It remains that in order to be consistent with the reminder disclosure of the application as filed, the sole possible reading is a concentration of the active component expressed in weight of active compound per volume of composition.

3.4 The Respondent further objected to that the passage of page 8 relating to the ophthalmological composition use was not disclosed in combination with the specific compounds (9).

However, the features relating to the ophthalmological composition for topical treatment of glaucoma or ocular hypertension are to be read in combination with any prostaglandin derivative disclosed in the application, thus inclusive compound (9).

3.5 Thus, the application as filed provides a proper basis for the subject-matter of claim 1 of the main request. Consequently, the requirement of Article 123(2) is fulfilled.

3.6 The present application was filed as a divisional application of European application 93109514.5, which

in turn was filed as a divisional application of European application 89850294.3.

The description of the application as filed is identical to that of both European applications 89850294.3 and 93109514.5. The support of claim 1 is based exclusively in the description of the application as filed. Thus, the requirement of Article 76(1) EPC is also satisfied for claim 1 of the main request.

- 3.7 Claim 1 as granted was directed to C₁-C₁₀ alkyl ester of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α , thus covering the 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α -isopropyl ester. Claim 1 of the main request is a Swiss-type claim directed to the use of this compound. Since the protection conferred by the product claim 1 as granted is larger than that conferred by the use claim 1 of the main request, the requirement of Article 123(3) EPC is therefore met, which finding was not contested.

4. *Clarity (Article 84 EPC)*

The appealed decision found claim 1 of the main request (then pending auxiliary request 7) met the requirement of Article 84 EPC (see point III above). Clarity was no longer contested in the appeal proceedings, nor does the Board see any reason to take a different view. Hence, it is unnecessary to go into more detail in this respect.

5. *Insufficiency of disclosure*

Although raised as ground for opposition by former opponents 3 and 4 against claim 1 as granted, this issue was no longer in dispute before the Board in view of the amendments made to the claim 1 of the main request. The Board is satisfied that the patent in suit discloses the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

6. *Novelty*

Lack of novelty raised as grounds for opposition by Respondent II and III against claim 1 as granted. In view of the amendments made to the claim of the main request, the Board is satisfied that the subject-matter of claim 1 is novel, already since none of the cited documents discloses the 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2 α -isopropyl ester.

7. *Inventive step*

7.1 *Closest prior art*

Document (7) relates to the correlation between the prostaglandin F2 α effects on rabbit intraocular pressure (IOP) and classical PGF2 α receptor stimulation. It discloses the IOP potency rank order of several PGF2 α derivatives including PGF2 α , 13-14 dihydro PGF2 α and 17-phenyl,18,19,20 trinor PGF2 α .

The Board considers, in agreement with the Appellant and Respondent II and III that this document represents

the closest prior art to the invention, and hence, the starting point for the assessment of inventive step.

In its notice of opposition, Respondent II indicated that documents (6) and (8) may also represent a starting point for inventive step. However, these documents relate to ester of PGF2 α which are structurally more remote to Latanoprost than the 17-phenyl,18,19,20 trinor PGF2 α disclosed in document (7). Therefore documents (6) and (8) are more remote to the claimed invention than document (7).

7.2 *Technical problem underlying the patent-in-suit*

The Appellant defined the technical problem underlying the invention as the provision of a further prostaglandin analogue having the ability to reduce intraocular pressure and treat glaucoma or ocular hypertension without exhibiting undesirable side effects, namely ocular irritation and hyperaemia.

7.3 *Solution*

As a solution to this problem, the patent-in-suit proposes Latanoprost which is characterized by a C-C single bond in position 13 and an isopropyl ester moiety.

7.4 *Success*

Tables V and VI of the patent-in-suit reveal that latanoprost (compound 9) had an intraocular pressure reducing effect, while tables III and IV showed the absence of ocular irritation and hyperemia for this

compound. The Board is therefore satisfied that the technical problem have been solved by the proposed solution.

7.5 *Obviousness*

Finally, it remains to be decided whether or not the proposed solution to the problem underlying the disputed patent is obvious in view of the cited prior art.

Document (7) teaches that specific PGF2 α derivatives, such as 13-14 dihydro PGF2 α and 17-phenyl-18,19,20 trinor PGF2 α have the ability to reduce intraocular pressure. However, this document does not tackle the problem of providing further derivatives, let alone gives any hint on how to achieve this goal. Hence, for this simple reason that document alone cannot point to the claimed solution for solving the technical problem underlying the patent-in-suit. Thus document (7) itself does not suggest the proposed solution.

In their notice of opposition, Respondents II and III argued that it was obvious to combine the structural characteristics of two PGF2 α derivatives to arrive at the compound of the invention. However, in the field of drug design any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, *a priori* expected to disturb the pharmacological activity profile of the initial structure (see T 643/96 point 4.2.3.3 of the reasons; T 548/91, point 6.4 of the reasons; both decisions not published in the OJ EPO).

Document (10) discloses that esters of PGF2 α derivatives reduce intraocular pressure. Accordingly, even by combining the teaching of document (7) with that of document (10), namely by esterifying the PGF2 α derivatives disclosed in document (7), the person skilled in the art would not have arrived at the solution proposed by the patent in suit which is also characterized by the presence of a single bond in position 13 of the PGF2 α derivative.

Therefore, the Board comes to the conclusion that the subject-matter of claim 1 involves an inventive step within the meaning of Article 56 EPC.

8. *Double patenting*

Although not being a ground for opposition, the Respondent I objected to double patenting, since claim 1 of the patent-in-suit was amended during the opposition/appeal proceedings in such a manner that its scope was fully encompassed by the scope of the claims of the patent EP0364417B granted from the grand parent application. The subject-matter of claim 1 of the patent-in-suit was not substantially different from the subject-matter of the combination of claims 1, 9 and 14 of EP0364417B for the contracting states AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE or of the combination of claims 1 and 15 for the contracting states ES and GR.

In G 1/05 (OJ EPO 2008, 271) and G 1/06 (OJ EPO 2008, 307) (both point 13.4 of the reasons), the Enlarged Board of Appeal accepted that a principle of prohibition of double patenting existed on the basis

that an applicant had no legitimate interest in proceedings leading to the grant of a second patent for the same subject-matter. This requirement of "same subject-matter" was followed in the established case law of the technical boards of appeal regarding the question of "double patenting" (see e.g. T 1391/07, point 2.5 of the reasons; T 877/06, point 5 of the reasons; T 1708/06, point 6 of the reasons; T 469/03, point 4.2 of the reasons, none published in OJ EPO).

In the present case, claim 1 of the patent-in-suit requires a treatment in a human being and a dose of 0.1 to 30 micrograms of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF₂α-isopropyl ester in 10 to 50 microlitres of the composition. These technical features are not required by any claim of EP0364417B. It follows that due to these technical distinguishing features the subject-matter of claim 1 of the patent-in-suit is not the same as that of claim 14 of EP0364417B.

Since EP0364417B and the patent in suit claim different subject-matter, the question of double patenting cannot arise.

Respondent I nevertheless referred to the headnote of T 307/03 (loc. cit.) which stipulates that a double patenting objection can also be raised where subject-matter of the granted claim is encompassed by the subject-matter of the claim later put forward.

The Board, however, sees no reason to depart from the mandatory requirement of "same subject-matter" invoked in the decisions G 1/05 and G 1/06 and in the established case law in relation with double patenting

to claims on the mere ground that the subject-matter of the claim later put forward is already encompassed in a granted claim.

This argument of the Respondent I must thus be rejected.

Auxiliary request

9. Since the main request is considered to be allowable, it is not necessary to decide on the lower-ranking auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside
2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the main request as filed with the letter dated 9 March 2012 (claim 1) and a description yet to be adapted.

The Registrar

The Chairman

C. Rodríguez Rodríguez

P. Gryczka