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Datasheet for the decision of 3 March 2023

Case Number: T 0553/20 - 3.3.07

Application Number: 14001862.3

Publication Number: 2772249

IPC: A61K9/08, A61K47/10, A61K47/26, A61K47/18, A61K31/5575

Language of the proceedings: EN

Title of invention:
Method and composition for treating ocular hypertension and glaucoma

Patent Proprietor:
SANTEN PHARMACEUTICAL CO., LTD.
AGC Inc.

Opponent:
Cooke, Richard

Headword:
Glaucoma/SANTEN

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

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It can be changed at any time and without notice

Keyword:
Inventive step - obvious solution
Amendment after summons - taken into account (no)

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Case Number: T 0553/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 March 2023

Appellant: (Patent Proprietor 1)	SANTEN PHARMACEUTICAL CO., LTD. 9-19, Shimoshinjo 3-chome Higashiyodogawa-ku, Osaka-shi, Osaka 533-8651 (JP)
Appellant: (Patent Proprietor 2)	AGC Inc. 5-1, Marunouchi 1-chome Chiyoda-ku Tokyo 100-8405 (JP)
Representative:	Müller-Boré & Partner Patentanwälte PartG mbB Friedenheimer Brücke 21 80639 München (DE)
Respondent: (Opponent)	Cooke, Richard Elkington and Fife LLP Patents Department 3-4 Holborn Circus London EC1N 2HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 January 2020 revoking European patent No. 2772249 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 772 249 ("the patent") was granted on the basis of sixteen claims.

The claims as granted related to an ophthalmic aqueous solution comprising a PGF2α analogue, a β-blocking agent, a nonionic surfactant, a stabilizing agent and substantially no preservatives in a container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene, wherein the polyethylene is low density polyethylene (LDPE).

II. The patent was opposed on the grounds that its subject-matter lacked an inventive step and that the patent comprised subject-matter extending beyond the content of the parent application.

The patent proprietors filed the appeal against the decision of the opposition division to revoke the patent. The decision was based on the main request and auxiliary requests 1 and 2 filed with the letter of 22 June 2018, auxiliary requests 3-9 filed with the letter of 8 July 2019 and auxiliary request 5* filed during the oral proceedings before the opposition division held on 9 September 2019.

Auxiliary request 5 related to a single claim which defined:

"An ophthalmic aqueous solution comprising 0.0010-0.0025% w/v tafluprost, timolol, 0.075% w/v polysorbate 80 [poly(oxyethylene) sorbitan monooleate],

0.005 - 0.2% w/v stabilizing agent, and optionally buffering agents, pH adjusters and tonicity agents conventionally used in ophthalmic solutions, and substantially no preservatives, in a single dose or unit dose container consisting essentially of polyethylene or in contact with container material consisting essentially of polyethylene, wherein the polyethylene is low density polyethylene (LDPE)."

In its decision the opposition division cited *inter alia* the following documents:

D1: EP 1 321 144 A
D12: Acta Ophthalmol; 2007; 85; s240
D13: Timoptic ® Data Sheet, 2005
D16: Guideline on the categorisation of extension applications (EA) versus variations applications (V), October 2003, European Commission

The opposition division concluded *inter alia* that the subject-matter claimed in accordance with auxiliary request 5 lacked an inventive step in view of document D1 as closest prior art.

III. With the statement of grounds of appeal the appellants (patent proprietors) filed a main request and auxiliary requests 1-5, which corresponded to the main request and auxiliary requests 1-5 on which the decision under appeal was based.

IV. The Board expressed in a communication pursuant to Article 15(1) RPBA *inter alia* the preliminary opinion that the subject-matter defined according to the main request and auxiliary requests 1-5 did not involve an inventive step.

V. With the letter of 2 February 2023 the appellants presented new experimental results concerning the bioavailability of tested formulations.

The respondent (opponent) argued in the letter of 10 February 2023 *inter alia* that the newly filed bioavailability data should not to be taken into account.

VI. Oral proceedings were held on 3 March 2023.

During the oral proceedings the appellants withdrew their main request and auxiliary requests 1-4 and only maintained auxiliary request 5 as their new main request.

VII. The arguments of the appellants relevant to the present decision are summarized as follows:

(a) Admittance additional experimental data

The additional bioavailability data presented in the letter of 2 February 2023 were filed in response to the Board's communication pursuant to Article 15(1) RPBA, in which it was observed that no bioavailability data for a composition comprising the 0.075% polysorbate 80 as claimed had been filed.

(b) Inventive step

The claimed subject-matter differed from the closest prior art represented by the composition of Table 7 in document D1 in (i) the nature of the material of the container, (ii) the single or unit dose form of the container, (iii) the lower

concentration of the tafluprost, (iv) the presence of timilol and (v) the higher concentration of the polysorbate 80.

The combination of these differences contributed to the solution of the objective technical problem of providing a formulation for the convenient administration of tafluprost which is free of preservatives and combines reduced absorption of tafluprost by the container with adequate bioavailability for an effective low dose of tafluprost. In this context figures 1-3 of the patent demonstrated the effect of the reduced tafluprost absorption resulting from the increased polysorbate 80 concentration, whilst figure 4 of the patent indicated reduced bioavailability of tafluprost from an increase in the polysorbate 80 concentration.

The skilled person would be aware that in comparison with multidose containers the single or unit dose containers defined in the claim of the remaining request are of a smaller size providing a larger surface to volume ratio. As indicated in the patent (see paragraph [0008]) the problem of absorption of tafluprost to the container wall was therefore particularly severe in case of a single or unit dose formulation. Moreover, the skilled person would be aware from document D1 of the inferior performance of polyethylene in comparison to polypropylene in terms of tafluprost absorption when used as a container material. The skilled person would further be confronted with the risk of reduced bioavailability when increasing the polysorbate 80 concentration. The issue of reduced bioavailability of tafluprost due to excessive

amounts of polysorbate 80 had not been recognized in document D1. Document D1 merely indicated that the concentration of the surfactant was preferably ten or more times that of the prostaglandine derivative and usually less 0.5%. Moreover, Figure 1 of document D1 demonstrated that without any polysorbate 80 tafluprost was already soluble up to a concentration of 0.002%, which indicated that at low tafluprost concentration as defined in the claim of the remaining request no advantage from an increase of the polysorbate 80 concentration was to be expected.

Faced with the above mentioned problem it would therefore not have been obvious to the skilled person to modify the composition of Table 7 from document D1 by choosing the inferior polyethylene material for a container of single or unit dose of a tafluprost solution having a more critical surface-volume ratio whilst combining the tafluprost with timilol and reducing its concentration and at the same time raising the concentration of polysorbate to an excess of thirty or more times the concentration of the tafluprost.

VIII. The arguments of the respondent relevant to the present decision are summarized as follows:

(a) Admittance additional experimental data

The filing of the bioavailability data with the appellant's letter of 2 February 2023 was not justified by cogent reasons in view of any exceptional circumstances, because the lack of bioavailability data for a composition covered by the claims had not only already been mentioned in

the reply to the appeal, but had even been explicitly considered in the reasons for the appealed decision.

(b) Inventive step

Starting from the composition of Table 7 of document D1 the skilled person would consider the claimed formulation obvious as a solution to the problem of providing an alternative practical implementation of the teaching of document D1.

As evidenced by documents D13 and D16 single or unit dose containers were well known in the field of ophthalmic formulations. The skilled person would therefore consider the provision of tafluprost in a single or unit dose an obvious practical alternative.

Document D1 specifically mentioned polyethylene as one of the preferred container materials and reported its only marginally lower performance in terms of absorption compared to polypropylene. Document D1 would therefore not dissuade the skilled person from the use of a container made of LDPE as defined in the claim of the remaining request.

Document D1 further described for the prostaglandine derivatives in general a concentration ranging from 0.00005 to 0.05% and mentioned in Table 1 specifically a tafluprost composition with a concentration of 0.001%. The concentration of tafluprost defined in claim was thus in line with the teaching of document D1.

The combination of tafluprost with timolol was obvious in view of document D12. In the context of the claimed invention no evidence of any unexpected effect from this combination had been provided.

The further reduction of tafluprost absorption from a solution with a polysorbate 80 concentration of 0.075% as compared to 0.05% demonstrated for the tested compositions in Figure 3 of the patent was obvious in view of document D1, which taught that nonionic surfactants such as polysorbate 80 reduce the absorption of prostaglindine derivatives such as tafluprost to containers made of a resinous material such as LDPE. The polysorbate concentration of 0.075% was in line with the teaching of document D1, according to which the concentration of the nonionic surfactant was preferably 10 times or more that of the prostaglandine derivative and usually less than 0.5%. Document D1 showed in Figure 1 the increased solubility of tafluprost depending on the polysorbate 80 concentration, which did not affect the considerations regarding the reduction of absorption. The reduced bioavailability of tafluprost at a polysorbate 80 concentration of 0.2% shown in Figure 4 would not dissuade the skilled person from using polysorbate 80 in the concentration of 0.075% as defined in the claim of the remaining request.

IX. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of their new main and only remaining request corresponding to auxiliary request 5 on which the decision under appeal was based.

X. The respondent requested that the appeal be dismissed.

The respondent further requested that the bioavailability data filed with the appellants' letter of 2 February 2023 not be admitted.

Reasons for the Decision

1. Admittance additional experimental data

The appellants filed with their letter of 2 February 2023 in response to the Board's communication pursuant to Article 15(1) RPBA additional results from experiments carried out in accordance with Example 2 of the opposed patent which demonstrated the bioavailability of tafluprost after administration of solutions comprising 0.0015% tafluprost in combination with polysorbate 80 at concentrations of 0.05%, 0.075% and 0.2%.

In its communication pursuant to Article 15(1) RPBA the Board observed that the patent does not provide bioavailability data for compositions with the defined polysorbate 80 concentration of 0.075%. However, the argument that no bioavailability data for a composition comprising the 0.075% polysorbate 80 as claimed were on file had already been raised in the respondent's reply to the appeal (see page 13, paragraph 99) and had been explicitly considered in the decision under appeal (see page 11, paragraph 1).

In view of this file history no exceptional circumstances justified with cogent reasons the amendment of the appellants' case involving the

additional bioavailability data filed with the letter of 2 February 2023. In view of Article 13(2) RPBA the Board has therefore decided not to admit these additional bioavailability data.

2. Inventive step

2.1 Closest prior art

The claimed subject-matter concerns solutions of tafluprost in a container comprising LDPE. According to the patent the absorption of the tafluprost by this container material is reduced by the presence of the nonionic surfactant polysorbate 80 (see paragraph [0018]).

Document D1 describes the use of a nonionic surfactants to enhance the solubility of prostglandine derivatives and to inhibit the absorption of the prostglandine derivatives by containers made of a resinous material (see D1, paragraph [0004]). In this context document D1 presents a stability test for an example of an ophthalmic solution (see D1, paragraphs [0031] to [0032]), which comprises 0.005 tafluprost, 0.05% polysorbate 80 and 0.05% EDTA salt (see Table 7) filled in a container made of polypropylene.

It was not in dispute that the composition of Table 7 of document D1 represented the closest prior art and that the claimed subject-matter differed from that composition in

(i) the nature of the material of the container (LDPE instead of polypropylene)

(ii) the single or unit dose form of the container,

(iii) the lower concentration of the tafluprost (0.0010 to 0.0025% instead of 0.005%)

(iv) the presence of timolol

(v) the higher concentration of the polysorbate 80 (0.075% instead of 0.05%).

2.2 Problem to be solved

The patent presents in Example 1 (see paragraphs [0035]to [0037]) an experiment involving the storage of unit doses of 0.3 ml of solutions comprising 0.0015% tafluprost in combination with 0.05%, 0.075% or 0.1% polysorbate 80 in an approximately 1 ml LDPE container. The results after 20 weeks storage at 40°C (see Figure 3) indicate for the solutions with 0.075% and 0.1% polysorbate 80 a reduced absorption of the tafluprost (ca. 88% remaining) compared to the solution with 0.05% (ca. 82% remaining). The patent further provides experimental results demonstrating the reduced bioavailability of tafluprost from a solution comprising 0.0015% tafluprost, when the polysorbate 80 concentration of the solution is raised from 0.05% to 0.2% (see Example 2, paragraphs [0038] to [0042] and Figure 4).

In view of these experimental results in the patent the Board finds no reason to doubt that the claimed subject matter may, in line with the formulation of the objective technical problem by the appellant, be considered to represent a solution to the problem of providing a formulation for the convenient administration of tafluprost which is free of preservatives and combines reduced absorption of

tafluprost by the container with adequate bioavailability for an effective low dose of tafluprost.

2.3 Assessment of the solution

2.3.1 As evidenced by document D16 (see page 9) and exemplified by document D13 (see page 1, under "DESCRIPTION") single or unit dose formulations were well known in the field of ophthalmic solutions. Such single or unit dose formulations represent as a matter of course convenient administration forms. Faced with the objective technical problem identified in section 2.2 above the skilled person would therefore as a matter of obviousness consider the possibility of adapting the composition of Table 7 in document D1 to a single or unit dose formulation.

2.3.2 Document D1 teaches explicitly that nonionic surfactants such as preferably polysorbate 80 (see D1, paragraph [0010]) inhibit the absorption of prostaglandine derivatives such as typically tafluprost (see D1, paragraph [0024]) by containers made of resinous material such as preferably polypropylene and polyethylene of the high or low density type (see D1, paragraph [0014]). In this context document D1 presents results of a stability test showing after six months storage at 40°C a remaining concentration of tafluprost of 72% in a polyethylene container and of 83% in a polypropylene container (see D1, paragraphs [0025] to [0026], Tables 1-2). In view of the effective absorption inhibition from polysorbate 80 described in document D1 the skilled person would not be discouraged from adapting the composition of Table 7 in document D1 to a single or unit dose formulation by the less favourable surface to volume ratio of such

formulations. Moreover, in view of the recommendation in document D1 that polyethylene represents a suitable and preferred container material, the skilled person would not be dissuaded from using polyethylene as a container material for a single or unit dose formulation on the basis of the reported marginally higher tafluprost absorption in a polyethylene container than in a polypropylene container. Faced with the identified objective technical problem the skilled person would therefore consider it an obvious solution to adapt the composition of Table 7 in document D1 by formulating it in a single or unit dose container made of LDPE as defined in the claim of the remaining request.

2.3.3 Document D1 describes for the concentration of the prostaglandines in general a range of 0.00005 to 0.05% (see D1, paragraph [0015]). As example of the intended compositions document D1 describes in addition to the composition of Table 7 comprising 0.005% tafluprost a composition comprising 0.001% tafluprost, be it without the EDTA (see D1, paragraph [0025], Table 1). Accordingly, the tafluprost concentration of 0.0010 to 0.0025% as defined in the claim of the remaining request corresponds to the suitable concentrations for tafluprost as described in document D1.

The combination of the tafluprost with timolol had already been described as providing additive effects for reducing intraocular pressure in patients with glaucoma in document D12 (see title). As pointed out by the respondent no evidence on file supports any unexpected effect from the combination of the tafluprost with timolol.

In adapting the composition of Table 7 of document D1 by formulating it in a single or unit dose container the skilled person would therefore consider the reduced concentration of the tafluprost and its combination with timolol as defined in the claim of the remaining request obvious variations of practical implementation.

2.3.4 Document D1 describes for the nonionic surfactant a concentration of preferably ten or more times the concentration of the prostaglandine derivative, which should in view of the potential for adverse effects from the nonionic surfactant normally not exceed 0.5% (see D1, paragraph [0016]). The increased polysorbate 80 concentration of 0.075% defined in the claim of the remaining request amounts to thirty or more times the tafluprost concentration and thereby still corresponds to a concentration of the nonionic surfactant in the range indicated as preferred in document D1.

Taking account of the purpose of the presence of the nonionic surfactant as described in document D1, in particular the inhibition of the absorbance of the prostaglandine derivative by the resinous container, it therefore required no more than routine experimentation to verify that an increased polysorbate 80 concentration of 0.075% further reduces the absorption of tafluprost when adapting the composition of Table 7 of document D1 for a single or unit dose formulation.

2.3.5 The appellants argued that according to Figure 1 of document D1 tafluprost is already soluble up to a concentration of 0.02% without the presence of a nonionic surfactant. According to the appellants the skilled person would therefore not expect any further effect from an increase in the concentration of the polysorbate 80 when the concentration of the tafluprost

is reduced to a level of 0.025% or lower as defined in the claim.

However, as pointed out by the respondent Figure 1 of document D1 concerns the effect of the nonionic surfactant on the solubility of the prostaglandine derivative and not the effect on the absorption of the tafluprost by the container. The effect of the nonionic surfactant on the absorption of the prostaglandine derivative is instead demonstrated in document D1 in Table 2 in relation to a composition comprising 0.001% tafluprost (see D1, paragraphs [0025] to [0026]). As explained in section 2.3.4 it required in view of this known effect of polysorbate 80 from document D1 no more than routine experimentation to verify the reduction of the absorption of tafluprost from the increased polysorbate 80 concentration of 0.075% as defined in the claim of the remaining request.

Accordingly, the appellants' argument based on the solubility data from Figure 1 of document D1 is not considered convincing.

2.3.6 The appellants further argued that the patent showed with the experimental results in Figure 4 involving solutions comprising 0.05% and 0.2% polysorbate 80 that the skilled person would be confronted with the risk of reduced bioavailability of the tafluprost when increasing the polysorbate 80 concentration. According to the appellants the skilled person would therefore not increase the polysorbate 80 concentration to 0.075% representing an excess of thirty or more times the concentration of the tafluprost as a matter of obviousness.

As explained in sections 2.3.4 and 2.3.5 above it required on the basis of document D1 no more than routine experimentation to verify that an increased polysorbate 80 concentration of 0.075% further reduces the absorption of tafluprost. The patent indeed demonstrates with the results in Figure 4 that a polysorbate concentration of 0.2% affects the bioavailability of tafluprost, which had not been recognized in the prior art. However, the discovery of this negative effect in a solution comprising 0.2% polysorbate 80 does not imply any contribution over the prior art associated with the claimed formulation comprising 0.075% polysorbate 80. At the same time, the prior art provided the skilled person with no reason to doubt that an ophthalmic solution comprising comprising tafluprost with 0.075% polysorbate 80 provided adequate bioavailability of the tafluprost.

The appellants' argument based on the bioavailability data from Figure 4 of the patent is therefore also not considered convincing.

2.3.7 Accordingly, starting from the composition of Table 7 of document D1 the skilled person would consider the claimed formulation obvious as a solution to the objective technical problem of providing a formulation for the convenient administration of tafluprost which is free of preservatives and combines reduced absorption of tafluprost by the container with adequate bioavailability for an effective low dose of tafluprost.

The Board therefore concludes that the claimed subject-matter lacks an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated