

Internal distribution code:

- (A) Publication in OJ
(B) To Chairmen and Members
(C) To Chairmen
(D) No distribution

**Datasheet for the decision
of 7 December 2011**

Case Number: T 1160/08 - 3.3.02

Application Number: 02799587.7

Publication Number: 1429780

IPC: A61K 31/57

Language of the proceedings: EN

Title of invention:

Method of treating middle ear infections

Patentee:

Alcon, Inc.

Opponent:

STRAWMAN LIMITED

Headword:

Treatment for Otitis Media/ALCON INC.

Relevant legal provisions:

EPC Art. 56
RPBA Art. 13

Keyword:

"Admissibility of late-filed evidence (no)"
"Inventive step - (yes)"
"Existence of an improved effect"

Decisions cited:

-

Catchword:

-



Case Number: T 1160/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 7 December 2011

Appellant: Alcon, Inc.
(Patentee) Bösch 69
D-6331 Hünenberg (CH)

Representative: Best, Michael
Lederer & Keller
Patentanwälte
Unsöldstrasse 2
D-80538 München (DE)

Respondent: STRAWMAN LIMITED
(Opponent) 34 Lovedon Lane
Winchester
Hampshire SO23 7NU (GB)

Representative: Meldrum, David James
D Young & Co LLP
120 Holborn
London EC1N 2DY (GB)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 5 May 2008
revoking European patent No. 1429780 pursuant
to Article 101(3) (b) EPC.

Composition of the Board:

Chairman: A. Lindner
Members: D. Boulois
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 429 780 based on application No. 02 799 587.7 was granted on the basis of a set of eleven claims. The sole independent claim reads as follows:

"1. Use of a combination of ciprofloxacin and dexamethasone for the preparation of an aqueous suspension composition for the treatment of otitis media and an open tympanic membrane in at least one ear by topical application of the composition into the ear canal of a patient's ear."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step.

III. The documents cited during the opposition and appeal proceedings included the following:

- (2) WO96/39146
- (4) WO01/122936
- (9) Cipro HC Physician's Desk ref. 2000
- (10) Dexamethasone Physician's Desk ref.
- (11) Experimental report
- (12) Transplantation, Brief Communications, vol. 29, No 5, 425-428, May 1980
- (13) Meikle & Tyler, The American Journal of Medecine, Vol. 63, 200-207, August 1977
- (14) External Otitis: A Challenge in Management, Peter Roland, Upper Respiratory, Head and Neck Infections, 2000

(15) Clinical Practice Guideline, Otitis Media with Effusion, Rosenfield et al, May 2004, Vol. 130, Number 5, 95-118

(16) Antonelli et al, Oncology & Neurology, 31:519-523, 2010

IV. In the decision pronounced during the oral proceedings on 19 February 2008, the European patent was revoked on the basis of the claims as granted as main request and on the basis of the claims of an auxiliary request filed with the letter dated 3 May 2007.

In said decision, the opposition division decided that the subject-matter of the main and the auxiliary requests was not inventive.

Document (2) was considered to be the closest prior art for both requests.

Claim 1 of the main request differed from this disclosure in as much as hydrocortisone was replaced by dexamethasone. When seeking an alternative, it was generally accepted that dexamethasone could be used in place of hydrocortisone; document (10) showed that dexamethasone was a synthetic analogue of hydrocortisone. The use of dexamethasone was therefore obvious.

Starting from document (2), the skilled person would not take the teaching of document (9) as an obstacle, and would obviously substitute hydrocortisone with dexamethasone, in an attempt to find an alternative, and arrive at the subject-matter of the granted claims under Article 56 EPC.

As regards auxiliary request 1, the treatment of "acute" otitis media was nothing more than a selection of patients. Such a selection did not result in any

technical effect over and above that which would have been expected from document (2). The auxiliary request was not inventive under Article 56 EPC.

- V. The patentee (appellant) lodged an appeal against that decision.
- VI. With a letter of 30 January 2009, the appellant filed document (11).
- VII. With a letter dated 25 November 2011 the opponent (respondent) submitted documents (12) to (16).
- VIII. With a letter dated 25 November 2011, the respondent made it known that he would not be represented at the oral proceedings set for 7 December 2011.
- IX. With a telefax dated 28 November 2011, the appellant requested that the submissions and the documents filed by the respondent with the letter dated 25 November 2011, be disregarded.
A postponement of the oral proceedings was requested in the event that the board of appeal intended to allow the new documents into the proceedings.
- X. With a telefax dated 30 November 2011, the board informed the parties that the oral proceedings scheduled for 7 December 2011 were maintained and appellant's arguments would be considered in the light of the discussion on admissibility of the documents pursuant to Article 13 of the RPBA.
- XI. Oral proceedings took place on 7 December 2011.

XIII. The appellant's arguments can be summarised as follows:

Document (2) discloses two different compositions, namely ciprofloxacin alone or in combination with hydrocortisone and two different medical indications, namely otitis externa and otorrhea (otitis media with ruptured ear drum causing effusion); the document does not mention which composition treats which indication. Furthermore, the tests of document (2) are performed only in view of testing the ototoxicity.

Document (11) is submitted to show that compositions comprising ciprofloxacin and dexamethasone in treating otitis media in chinchillas, which is a well-acknowledged animal model for acute otitis media with open tympanic membrane, are far superior to the compositions of document (2) comprising hydrocortisone and ciprofloxacin. The volume of the middle ear effusion is significantly reduced with a combination of ciprofloxacin and dexamethasone over ciprofloxacin-hydrocortisone.

Furthermore, the efficacy of compositions comprising ciprofloxacin and dexamethasone is dependent on the concentration of dexamethasone, while in the compositions of document (2) the efficacy is not dependent on the concentration of hydrocortisone and thus cannot be improved by adjustment of the concentration of hydrocortisone.

In view of the experiments described in document (11), the problem of providing a composition for treating otitis media with an open tympanic membrane with a superior effect to the compositions of document (2) has been solved by the contested patent.

None of the documents on file discloses that the combination of ciprofloxacin and dexamethasone could be useful for treating otitis media, or be advantageous over the compositions of document (2).

XIII. The respondent's arguments can be summarised as follows:

Documents (12)-(16) are submitted to clarify the common knowledge at the priority date and the nature of the animal model used by the appellant in document (11). A therapeutic improvement would have been expected in the light of what was known at the priority date of the contested patent. Document (10) teaches that 0.75 mg of dexamethasone is equivalent to about 20-25 mg of hydrocortisone, illustrating that dexamethasone is more efficacious than hydrocortisone. A replacement of hydrocortisone by dexamethasone would unsurprisingly provide a more effective composition. Documents (12), (13) and (14) are submitted to substantiate this point. The experiments reported in document (11) do not assess the effectiveness of the composition in a model involving an open tympanic membrane as required by the claims, since this document is silent about otitis media with an open tympanic membrane. The model used in document (11), namely otitis media with effusion, is not the same as otitis media with an open tympanic membrane. Documents (15) and (16) are submitted to illustrate that the model used in document (11) is not appropriate.

XIV. The appellant requested that the decision under appeal be set aside and the patent be maintained unamended (main request) or, alternatively, as amended according to the auxiliary request filed with the statement of

the grounds of appeal. The appellant further requested that documents (12) to (16) not be admitted into appeal proceedings or, alternatively, to postpone oral proceedings.

XV. The respondent requested in writing that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.
2. Admission of documents (12), (13), (14), (15) and (16).

Documents (12), (13), (14), (15) and (16) were submitted by the respondent with a letter dated 25 November 2011, shortly before the oral proceedings scheduled for 7 December 2011 and therefore at a very late stage of the appeal proceedings. Their admissibility is therefore at the board's discretion and depends on the overall circumstances of the case. According to Article 13(1) RPBA, this discretion depends inter alia on the complexity of the new evidence submitted, the current state of the proceedings and the need for procedural economy. The documents were filed in response to the experiments performed by the appellant, filed on 30 January 2009, more than two years before.

The documents were late-filed. The respondent did not provide any justification in the letter of 25 November 2011 for this late-filing, and did not explain why it had not been possible to file the documents earlier.

The appellant objected to the admissibility of the new documents. A postponement of the oral proceedings scheduled for 7 December 2011 was requested to provide more time to study the documents submitted and evaluate their relevance, assuming that the documents were to be admitted into the proceedings by the Board.

Under these circumstances, the board decided to not admit documents (12), (13), (14), (15) and (16) into the proceedings (Article 13 RPBA).

3. Main request - Inventive step:

The present invention concerns the treatment of otitis media and an open tympanic membrane by a combination of ciprofloxacin and dexamethasone (see paragraphs [0001], [0003], [0010] and examples 2,3 of the contested patent).

- 3.1 Document (2) is concerned with the treatment of otitis media and specifically otorrhea, which is an otitis media with ruptured ear drum causing effusion (page 1, lines 8-9; page 4, lines 19-26). The treatment is effected by ciprofloxacin alone or in combination with an anti-inflammatory agent, preferably hydrocortisone (page 5, lines 22-25; example 5).

The board concludes that document (2) constitutes the closest prior art. This was not contested by any party.

- 3.2 In defining the technical problem vis-à-vis document (2), and in particular in determining whether or not the subject-matter as defined in present claim 1

constitutes an improvement, an alternative or merely a further embodiment, the experiments of document (11) provided by the appellant-proprietor need to be discussed.

Document (11) provides comparative data between a control composition, and four compositions comprising ciprofloxacin and either hydrocortisone or dexamethasone, each of the latter being present at concentrations of 0.1 or 1% in the compositions. The purpose of this document is to compare the technical teaching of the contested patent with the teaching of document (2), and to demonstrate the existence of an improved effect.

- 3.2.1 The animal model used by the appellant is a lipopolysaccharide-induced experimental otitis media with effusion in chinchilla. Effusion was induced by the injection of a bacteria shoot of *Pseudomonas aeruginosa* in the superior bullae of the chinchillas. As mentioned in paragraphs 2 and 3 of the contested patent, *Pseudomonas aeruginosa* are bacteria typically present in the otitis externa infection. When the tympanic membrane ruptures, the bacteria characteristic of otitis externa and media mix. The injection of the shoot of *Pseudomonas aeruginosa* allows a simulation of an otitis media with open tympanic membrane. The chosen model allows one to choose which bacteria may be injected within the chinchilla's ears. The board sees no reason to question the relevance of the experimental model used in document (11). The purpose of the test is to measure the effect of the anti-inflammatory drug, which is related to the effusion volume. The test used simulates the situation

of an otitis media with open tympanic membrane with typical bacterial infection. A rupture of the tympanic membrane does not seem necessary to provide conclusive results for the action of an anti-inflammatory in an experimental model for otitis media with open tympanic membrane.

- 3.2.2 The results provide by document (11) allow a comparison between compositions comprising ciprofloxacin and hydrocortisone at concentrations of 0.1 and 1% and compositions of ciprofloxacin and dexamethasone at the same concentrations of 0.1 and 1%. Each composition is given in the same quantities.

The results show a better effect for all compositions comprising dexamethasone over hydrocortisone. The compositions at 0.1% or 1% show an improved effect on the effusion against composition comprising hydrocortisone at the same concentration. Furthermore, the results obtained with dexamethasone at 0.1% are significantly better than the results obtained by hydrocortisone at a concentration of 1% (Figure 2).

- 3.2.3 In view of the evidence provided by document (11) for an improvement vis-à-vis the closest prior art, the problem underlying the present invention can be seen as the provision of a composition for improved treatment of otitis media and an open tympanic membrane.

The proposed solution to this problem is the use of the compositions as defined in claim 1, characterised by the combination of ciprofloxacin and dexamethasone.

As mentioned above, document (11) shows that the problem has been solved concretely at concentrations of dexamethasone of between 0.1 and 1%.

Given the supposed high potency of dexamethasone, it is to be expected that a high anti-inflammatory effect is observed for the entire range of effective anti-inflammatory concentrations envisaged by the skilled person. This anti-inflammatory effect is credibly superior to the effect observed with hydrocortisone, since the effect of the latter is lower at a concentration as high as 1% and is expected to decline below a concentration of 0.1%.

The board concludes that the problem is solved over the whole scope of claim 1.

- 3.3 Thus the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.
- 3.3.1 The respondent argued that, starting from the teaching of document (2), the skilled person would have expected a superior effect by the substitution of dexamethasone for hydrocortisone in the light of document (10), which shows that the difference of potency for oral dexamethasone versus hydrocortisone is at least about 25 fold. This document, however, only deals with oral administration for which parameters such the half-life of the product or the absorption plays a role. There is no evidence on file that similar results could be obtained with topical or mucosal administration. As a consequence, the teaching of document (10) cannot be extended to the present invention. The improved effect

obtained by the use as per claim 1 as granted was therefore not foreseeable by the skilled person.

An increase of the effect with concentrations of hydrocortisone higher than 1% is also not credible in view of the ceiling of the effect as shown in Figure 2 of document (11).

3.3.2 It is additionally noted that the improved effect is not observed for any otic affection but is restricted to the specific otic disease according to claim 1 as granted. This is demonstrated by example 2 of the contested patent, which shows that a composition of ciprofloxacin and dexamethasone is not more efficient than ciprofloxacin alone for the treatment of acute otitis externa.

3.3.3 As a consequence, document (4), which relates to topically administrable stable ophthalmic and otic compositions comprising a combination of dexamethasone and ciprofloxacin (page 1, lines 6-10), but is silent on the specific medical indications to be treated, is not pertinent.

3.3.4 An improved effect on otitis media with an open tympanic membrane could therefore not be expected in the light of the prior art.

3.4 The requirements of Article 56 EPC are therefore met for the Main Request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is maintained unamended.

The Registrar:

The Chairman:

N. Maslin

A. Lindner