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**Datasheet for the decision
of 31 July 2013**

Case Number: T 0070/10 - 3.3.02

Application Number: 00921047.7

Publication Number: 1173177

IPC: A61K 31/436, A61P 27/02

Language of the proceedings: EN

Title of invention:
Use of macrolide compounds for the treatment of dry eye

Patent Proprietor:
Sucampo AG

Opponent:
NOVARTIS AG

Headword:
Use of macrolides for the treatment of dry eye/SUCAMPO

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Main request (allowable)"

Decisions cited:
-

Catchword:
-



Case Number: T 0070/10 - 3.3.02

DECISION
of the Technical Board of Appeal 3.3.02
of 31 July 2013

Appellant: NOVARTIS AG
(Opponent) Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel (CH)

Representative: von Sprecher, Georg
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Respondent: Sucampo AG
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
12 November 2009 concerning maintenance of
European patent No. 1173177 in amended form.

Composition of the Board:

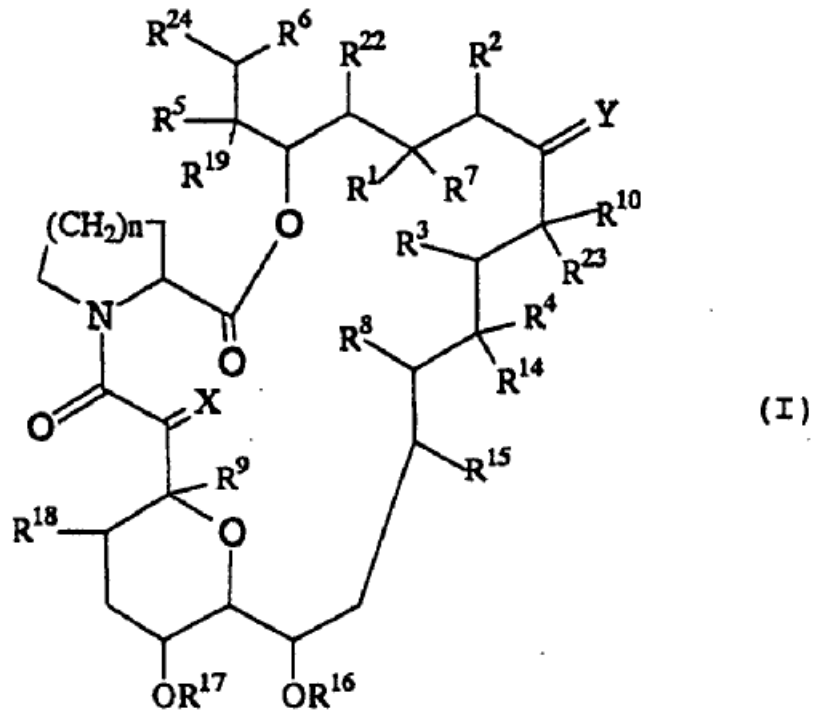
Chairman: U. Oswald
Members: M. C. Ortega Plaza
R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 173 177, based on European patent application No. 00921047.7, which was filed as an international patent application published as WO 00/66122, was granted with three claims.

Claim 1 as granted read as follows:

"1. Use of a macrolide compound for the manufacture of a pharmaceutical agent for the treatment of dry eye by local administration to the eye, wherein the macrolide compound is a tricyclo compound of the following formula (I)



wherein

adjacent pairs of R¹ and R², R³ and R⁴, and R⁵ and R⁶ each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{22} and R^{23} each independently show hydrogen atom or alkyl;

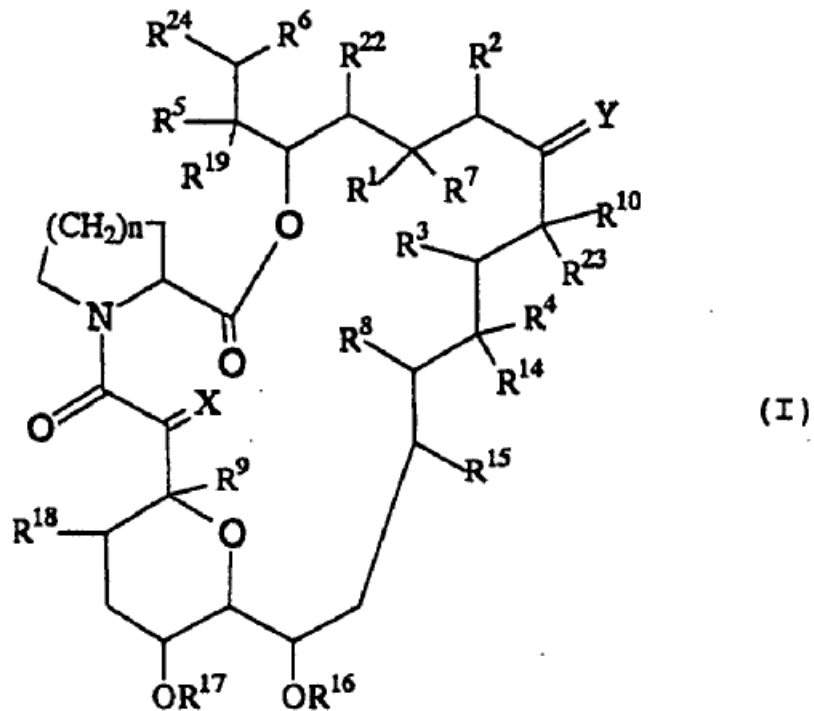
R^{24} is an optionally substituted ring which optionally contains one or more heteroatom(s); and

n is 1 or 2,

wherein Y, R^{10} and R^{23} optionally form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof."

Independent claim 3 as granted read as follows:

"3. Use of a macrolide compound for the manufacture of a pharmaceutical agent for the improvement of the tear film breakup time by local administration to the eye, wherein the macrolide compound is a tricyclo compound of the following formula



wherein

adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R¹⁰ is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, or alkyl substituted by oxo;
X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula -CH₂O-;
Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula N-NR¹¹R¹² or N-OR¹³;
R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl;
R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl;
R²⁴ is an optionally substituted ring which optionally contains one or more heteroatom(s); and
n is 1 or 2,
wherein Y, R¹⁰ and R²³ optionally form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula -CH₂Se(C₆H₅), and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof."

II. Opposition was filed and revocation of the patent in its entirety was requested in particular pursuant to Articles 100(a) and (b) EPC (the subject-matter of the opposed patent is not new, does not involve an inventive step, relates to subject-matter which is excluded from patentability - Article 52(4) EPC 1973 - and is insufficiently disclosed).

III. The following documents were cited *inter alia* in the opposition and appeal proceedings:

- D1 WO 97/25977
- D2 Yang et al., Pathology International
February 1999; 49; 133-140
- D3 K. Tsubota, International Ophthalmology Clinics,
1994; 34; 115-128
- D4 WO 92/19278
- D6 WO 96/31514
- D8 EP 0406791
- D12 Kaswan et al., Arch Ophthalmol 1989; 107; 1210-
1216

IV. The present appeal lies from an interlocutory decision of the opposition division maintaining the patent in amended form on the basis of the first auxiliary request filed at the oral proceedings before the opposition division (Articles 101(3) (a) and 106(2) EPC).

V. The opposition division considered that the objections against the patentability of the claimed subject-matter within the meaning of Article 52(4) EPC 1973 (Article 53(c) EPC 2000) were not well founded. Additionally, the opposition division considered that there was sufficiency of disclosure (Article 83 EPC) since the patent in suit taught that dry eye was diagnosed *inter alia* by lacrimal fluid evaluation tests, such as tear film breakup time (TFBUT) and example 2 indicated how the TFBUT was determined. Moreover, the opposition division stated that the method described in the patent in suit was a conventional method commonly used in ophthalmology.

The opposition division considered that the subject-matter claimed in the main request (set of claims as

granted) met the requirements of novelty over the cited prior art, in particular owing to the mode of administration defined in the claims as "local administration to the eye".

The opposition division considered that the subject-matter of claims 1 and 2 as granted lacked an inventive step. It defined document D3 as the closest prior art and the problem to be solved as to provide an alternative treatment for dry eye. The opposition division was of the opinion that the claimed solution was obvious in the light of document D3, alone or in combination with documents D4 and D8.

The first auxiliary request filed at the oral proceedings before the opposition division contained one single claim, namely claim 3 as granted. Therefore, the opposition division's findings in relation to Articles 83 and 54 EPC for the main request directly applied. Additionally, the opposition division considered that the subject-matter claimed in the first auxiliary request involved an inventive step (Article 56 EPC), since the only document which made reference to defects in the tear film as the primary mechanism for dry eye was document D3. However, document D3 did not teach how to arrive at the claimed solution.

- VI. The opponent (appellant) filed an appeal against said decision, and grounds thereto. With its grounds of appeal the appellant filed document D12. The appellant requested that the decision under appeal be set aside and the patent revoked in its entirety.

VII. The respondent (patent proprietor) filed a response to the appellant's grounds of appeal. It requested that the appeal be dismissed (i.e. maintenance of the patent in amended form on the basis of the set of claims filed as first auxiliary request at the oral proceedings before the opposition division) and gave reasons thereto.

VIII. The board sent a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings, expressing a preliminary opinion of the board.

In said communication the board analysed claim 1 of the set of claims filed at the oral proceedings before the opposition division and considered that it addressed the symptomatic improvement of dry eye concerning lacrimal fluid which was to be achieved by local administration to the eye. Moreover, the board pointed out that the local administration to the eye mentioned in the claim was not limited to the use of drops applied to a local site in the eye, but included as well the use of other dosage forms suitable for local administration to the eye such as ointments (see paragraph [0035] of the patent in suit).

The board mentioned in said communication that the appellant had not sufficiently substantiated in its grounds of appeal a lack of novelty of the subject-matter claimed.

Moreover, the board's communication also contained some observations in relation to Articles 56 and 83 EPC.

IX. With a letter dated 28 June 2013 the respondent filed an auxiliary request (first auxiliary request).

Claim 1 of the first auxiliary request reads as follows:

"1. Use of a macrolide compound for the manufacture of a pharmaceutical agent for the improvement of tear film breakup time by local administration to the eye, wherein the macrolide compound is FK506."

X. With a letter dated 23 July 2013 the appellant informed the board that it would not be attending the oral proceedings and confirmed that it requested that the patent be revoked.

XI. Oral proceedings took place on 31 July 2013 in the absence of the appellant.

XII. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows.

(a) Sufficiency of disclosure

Claim 1 specified the use of an active compound of formula (I) in the manufacture of a pharmaceutical agent for the improvement of tear film breakup time. Example 2 provided a specific formulation for FK506, based on that of document D8. Document D8 acknowledged the difficulty of formulating actives including FK506 in ophthalmic formulations and the drawbacks of traditional formulations (page 4, lines 36-51), including clinical usefulness (page 4, line 42). Therefore, it could be seen from document D8 that to provide the formulation of FK506 suitable for

ophthalmic applications was challenging and beyond mere routine modification within the ability of the skilled person. Claim 1 of the main request covered the use of this active in the manufacture of any other formulation without providing sufficient information to enable the skilled person to extend the teaching of the cited prior art to other formulations.

(b) *Inventive step*

Document D3 represented the closest prior art since it disclosed the use of Cyclosporin A in the treatment of dry eye by local administration. D3 further taught FK506 to be an obvious alternative to Cyclosporine A (mentioned as having the same mechanism of action).

The paragraph under the heading "Immunotherapy" on page 124 of document D3 taught that in cases where dry eye had an immunological component, this component manifested itself in defects in the tear film layer and, thus, dry eye could be treated by addressing the underlying immunological cause rather than by treating the symptoms with artificial tears (e.g. dry eye caused by Sjödren's syndrome, where lymphocyte infiltration into the lacrimal gland causes glandular dysfunction with resulting dry eye due to reduced tear formation). Therefore document D3 suggested that curing a defect in the tear film layer could be carried out by immunological modulation of the dry eye. Document D3 further disclosed how the immunosuppressant Cyclosporin A (to which FK506 was an obvious alternative) could be used in the treatment of canine dry eye. In addition document D12 (which corresponded to reference [8] in the above cited passage of

document D3) showed that the immunosuppressive effect of Cyclosporin A treated keratoconjunctivitis sicca (KCS, a synonym for dry eye) by increasing tear production as measured by the Schirmer's Tear Test (STT) (D12, abstract, lines 4-11), which was a measure of tear production. Increased tear production as measured by STT would be expected to correlate with improved tear film breakup time since an increase in tear production would give a thicker tear film on nictitation, which in turn would take longer to break. Document D12 stated on page 1212 that diagnosis of KCS was typically made using the STT, but changes in tear breakup time could also be used. The patent in suit categorised the STT and the tear film breakup time test (TFBUTT) as two of the main lacrimal fluid evaluation tests for use in the evaluation of dry eye.

Document D12 taught that the use of cyclosporin A in the treatment of dry eye by local administration gave improved tear production as measured by the STT and it was reasonable to assume that it correlated with improved tear film breakup time. The proposed solution was obvious since FK506 was an obvious alternative to cyclosporin. Therefore, the claimed subject-matter lacked an inventive step.

Moreover, the subject-matter of claim 1 of the main request concerned an "unduly broad generalisation" of the data in example 2 since the presumption of preservation of the activity over all compounds of formula I was not credible given the number of structural variables in formula (I) and the number of possible values that each could take. If the effect concerning the mechanism of FK506 improvement of tear film breakup time was considered to be unpredictable

even with the knowledge of FK506's use in the treatment of dry eye, the alternative mechanism was unknown and thus the effect exhibited by FK506 in example 2 of the opposed patent was not generalisable over the whole scope claimed.

XIII. The respondent's arguments, as far as relevant for the present decision, may be summarised as follows.

(a) *Sufficiency of disclosure*

Example 2 of the patent in suit referred to a formulation of FK506 according to document D8. This fact, however, did not allow the conclusion to be drawn that FK506 was difficult to formulate in ophthalmic formulations at the effective filing date of the patent in suit. Prior art D8 was filed on 3 July 1990 and claimed a priority date of 5 July 1989. This meant that document D8 defined at most the state of the art at a point of time about 10 years before the effective date of the patent in suit (relevant point of time for establishing whether or not there was sufficiency of disclosure). Moreover, document D8 itself disclosed a workable solution to the problem of providing ophthalmic formulations of FK506, namely by using a water-soluble solubiliser. This was also the case of the examples in the patent in suit. Moreover, document D8 disclosed that there were many known solubilisers which could be used to prepare ophthalmic formulations of FK506 (page 6, lines 2 to 7).

The medical indication and the technical effect addressed by claim 1 of the main request were disclosed in paragraph [0003] of the patent in suit, where it was

explained that TFBUTT, which was a lacrimal evaluation test, reflected the stability of precorneal tear film, and meant the time (sec) from complete nictitation to the initial breakage of the precorneal tear film. In the case of severe dry eye, the breakage of tear film occurred immediately after nictitation, which was rated as TFBUT zero (0) sec. Thus, the improvement of the TFBUT mentioned in the claim had to be understood within this context, as well as in the light of the disclosure in paragraphs [0045] and [0046] of the patent in suit. The respondent also cited board of appeal decision T 81/87, OJ EPO 1990, 250.

(b) *Inventive step*

The respondent referred to the board's communication sent as an annex to the summons to oral proceedings and stated that the question of whether the problem was solved within the whole scope claimed was a question of plausibility, and cited board of appeal decision T 1329/04 of 28 June 2005. Document D3 represented the closest prior art. The problem to be solved was to provide an alternative method or formulation for improving the TBUT.

Document D3 disclosed several approaches to dry-eye therapy. The second approach concerned new artificial tears (summary and pages 118 to 121). This approach revealed a concern with the mechanisms of tear film stability on the ocular surface rather than simply the maintenance of a certain tear volume (summary). The therapy with RGD peptide belonged to the approach of new artificial tears (page 120). Document D3 stated that RGD and chondroitin sulfate could mediate adhesion to the corneal epithelium and prolongation of the TFBUT.

A further approach disclosed in document D3 was immunotherapy. Document D3 mentioned that cyclosporine A or FK506 suppressed cytolytic T-cell function. However, document D3 disclosed the treatment of dry eye on the basis of experimental results (*in vitro* and in canine dry eye) for cyclosporine A only.

The respondent cited board of appeal decision T 385/07 of 5 October 2007, point 16 of the reasons, and stated that the skilled person would not be in a position to predict whether or not FK506 would be effective in the treatment of dry eye. It also cited board of appeal decision T 158/96 of 28 October 1998. In relation to this point the board asked about document D2 (which was mentioned in the list of documents in the opposition division's decision and had been published shortly before the effective filing date of the patent in suit). The respondent replied that document D2 disclosed FK506 as an immunosuppressive agent for the treatment of Sjögren's syndrome, characterised by dry eyes and a dry mouth due to molecular cell infiltration into the lacrimal and glandular glands which resulted in glandular dysfunction. However, document D2 did not disclose any effects on lacrimal fluid by topical treatment to dry eye.

Document D12 concerned cyclosporine topically used for the treatment of keratoconjunctivitis sicca (KCS) but did not refer to FK506. KCS was characterised as an immune-mediated disorder that had an influence on tear production. Thus, cyclosporine showed a quantitative effect on tear production. However, there was an essential difference between the quantity of tears and the quality of tear film. This difference was mentioned

in document D3 (pages 115, 120, 124). The quality of tear film had to do with stability of the film on - and its adhesion to - the ocular surface. It could not be concluded that an increase in tear production would render the tear film more adhesive. Therefore, the skilled person would not be able to derive from the content of documents D3 and D12 what the quality of the tear film produced would be.

As regards the question whether the problem had been plausibly solved, the respondent argued that the technical effect had been shown in example 2 for a representative compound of formula I, namely tacrolimus (FK506). Tacrolimus was representative for the macrolide compounds of formula I, which shared the macrolide skeleton with three integrated cyclic moieties. The structural variations represented a reasonable generalisation of the tested compound. The respondent cited paragraphs [0021] to [0025] of the patent in suit and specifically mentioned Ascomycin and Pimecrolimus.

XIV. The appellant (opponent) requested that the decision under appeal be set aside and European patent No. 1 173 177 be revoked.

The respondent (patentee) requested that the appeal be dismissed, or, alternatively, that the decision under appeal be set aside and the patent maintained in amended form on the basis of the first auxiliary request filed with the letter dated 28 June 2013.

Reasons for the Decision

1. The oral proceedings before the board took place in the absence of the appellant who was duly summoned but decided not to attend as announced with its letter dated 23 July 2013.

The present decision is based on facts and evidence on which the appellant has had an opportunity to comment. Therefore, the conditions set forth in Enlarged Board of Appeal opinion G 4/92, OJ EPO 1994, 149, are met.

Moreover, as stipulated by Article 15(3) RPBA, the board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case.

2. *Admissibility*

- 2.1 The appeal is admissible.

- 2.2 *Admissibility of the request filed with the letter dated 28 June 2013*

The first auxiliary request was filed as a direct reply to the board's communication sent as an annex to the summons to oral proceedings. This set of claims contains one single claim which corresponds to the use of one single macrolide compound, namely FK506.

The appellant has not raised any objection against the admission of the (first) auxiliary request.

Moreover, this request is simple to handle. Therefore, the first auxiliary request filed with the letter dated 28 June 2013 is admitted into the proceedings.

3. *Main request*

3.1 *Sufficiency of disclosure*

The patent in suit illustrates the claimed invention. An ophthalmic formulation suitable for topical application to the eye, which is produced following the method disclosed in example 6 of document D8, is exemplified in example 1 (0.06% eye drops suspension of FK506 containing *inter alia* polyvinyl alcohol). A further ophthalmic formulation (0.01% eye drops suspension FK506) was produced in example 2 following example 1. Compound FK506 (tacrolimus), used in the examples, is a representative macrolide compound of formula I. Moreover, example 2 illustrates the modus of application to the eye (instillation four times a day for 7 days) and the technical effect achieved, namely improvement of the tear film breakup time (which reflects the quality of the tear film and its adhesion to the ocular surface).

The arguments provided by the appellant do not raise serious doubts about the reproducibility of the claimed invention as regards the provision of formulations suitable for the topical ophthalmic use claimed. In particular, there is no technical evidence on file to support the assertion that the skilled person following

the teaching of document D8 and the information in examples 1 and 2 of the patent in suit would not be able to reproduce ophthalmic formulations suitable for the claimed use. Additionally, the TFBUT test is a conventional method well known in the art and it is disclosed in detail in example 2 of the patent in suit (paragraph [0046], see also paragraph [0003]).

Therefore, the patent in suit discloses the invention claimed in the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

3.2 *Novelty*

The novelty of the subject-matter claimed in the main request was acknowledged by the opposition division and the board sees no reason to differ.

The board made it clear in the communication sent as an annex to the summons to oral proceedings that the appellant had not provided any substantive arguments in support of the lack of novelty objection raised with the grounds of appeal. The appellant did not submit any arguments in relation to this issue in its reply dated 23 July 2013.

3.3 *Inventive step*

- 3.3.1 Document D3, which discloses several approaches to dry-eye therapy addressing *inter alia* tear production and tear film defects in dry eye by means of topical administration, represents the closest prior art (summary on page 115).

Document D3 discloses that "immune-targeted eye drops can modify the lymphocytic activities in the conjunctiva and lacrimal gland" and that "cyclosporine A has been reported to be effective for the treatment of canine dry eye" (summary on page 115).

Under the heading "Immunotherapy" document D3 discloses that "although the primary mechanism of dry eye is a qualitative or quantitative defect in the tear film layers, some types of dry eye are caused by immunological disorders, such as lymphocyte infiltration into the lacrimal gland and conjunctiva in Sjögren's syndrome" (page 124).

Document D3 further discloses that cytolytic T-cells mediate lacrimal gland destruction and that "cytolytic T-cell function can be suppressed with cyclosporin A or FK506 following kidney transplantation", and that "similar immunological modulation is being investigated to treat Sjögren's syndrome" (page 124). Moreover, document D3 discloses that "cyclosporine A is a potent drug capable of suppressing the cytolytic T lymphocyte" and that "it has shown promise in vitro and in the treatment of canine dry eye" (page 124).

Additionally, document D3 discloses dry-eye therapy by topical administration to the eye of artificial tears containing RGD peptide (consisting of arginine, glycine and aspartate) for prolonging the tear film breakup time by mediating adhesion to the corneal epithelium (page 120).

3.3.2 In the light of the closest prior art the problem to be solved lies in the provision of an alternative method for prolonging the tear film breakup time by topical administration to the eye.

3.3.3 The solution defined in claim 1 is to use a macrolide of formula I.

The board is satisfied that the problem has been plausibly solved in view of the test results shown in example 2 for the topical application to the eye of FK506 (tacrolimus). Tacrolimus is a representative compound of the macrolide compounds of formula I since it shares with the other compounds encompassed by formula I the main structural features essential for defining this particular class of macrolides, in particular the macrolide skeleton and the three cyclic moieties integrated thereto.

3.3.4 It has now to be investigated whether the proposed solution is obvious in the light of the cited prior art.

Document D3 teaches dry-eye therapy by topical administration of cyclosporine A based on its immunological modulation and mentions FK506 as a possible alternative in view of its immunological action. However, document D3 does not specify the technical effects achieved by the treatment of cyclosporine A to the defect in the tear film layers (quantitative or qualitative). Document D3 directly refers to document D12 (cited in document D3 as reference [8]).

Document D12 discloses the treatment of keratoconjunctivitis sicca (KCS) (dry eye) with cyclosporine eye drops. Document D12 teaches that, when treating canine eyes suffering from KCS with ophthalmic cyclosporine, cyclosporine increases tear production (summary on page 1210). Document D12 also teaches that topical administration allows cyclosporine to penetrate readily into the lacrimal glands (pages 1210, 1214) and that significant secretory activity has been seen after treatment with cyclosporine (page 1214). The ophthalmic test employed for measuring the technical effect of increased tear production/secretion in document D3 is the Schirmer's tear test (STT) (page 1214, summary on page 1210).

Document D3 does not mention any improvement in the quality of the tear film and its adhesion to the ocular surface. Moreover, document D3 teaches that "the time period that lapsed between initial treatment and initial effect suggests immunosuppression, but the lapses between stopped treatment and stopped effect, and restarted treatment and regained effect, suggest another mechanism of action for topical cyclosporine in tear production" (page 1214, right-hand column).

Therefore, apart from the fact that there are essential structural differences between the cyclic oligopeptides cyclosporine A to G and the macrolide compounds of formula I, a commonality in their immunological action does not suffice in the light of the teaching in document D12 for the skilled person to be able to expect a positive effect in the tear film production and/or quality of the tear film by topical application to the eye of the macrolide FK506.

Moreover, the knowledge reflected in the cited prior art does not show that the hint given to the skilled person in document D3 about the suppression of the cytolytic T-cell function could be directly linked to the technical effect concerning tear film quality and its adhesion to the ocular surface shown by improvement in the TFBUTT.

Document D2 discloses the use of FK506 as an immunosuppressive agent for the treatment of Sjögren's syndrome. However, the immunosuppressive treatment disclosed in document D2 does not concern topical treatment to dry eye (FK506 solution is administered by three intraperitoneal injections per week, see page 134) The treatment disclosed in document D2 addresses *inter alia* the injured lacrimal and salivary glands. In fact, document D2 teaches that the treatment suppresses mononuclear cell infiltration in the lacrimal and submandibular glands (page 137) but is silent about the possible effects on lacrimal film layer defects.

Therefore, the proposed solution is not rendered obvious by the cited prior art.

- 3.3.5 As regards the appellant's submission that an increase in tear production measured by STT would be expected to correlate with improved tear film break up time (TFBUT) measured by TFBUTT, the prior-art documents do not show that improvement of TFBUT is a direct consequence of an increase in tear film production/secretion. On the contrary, document D3 makes a clear distinction between qualitative and quantitative defects in tear film fluid (pages 120, 124).

3.3.6 Consequently, the subject-matter claimed in the main request meets the requirements of inventive step (Article 56 EPC.

4. Since the main request has been found to be allowable there is no need to deal with the first auxiliary request filed with the letter dated 28 June 2013.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

U. Oswald