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**D E C I S I O N**  
**of 25 September 2002**

**Case Number:** T 0112/99 - 3.3.2

**Application Number:** 91115360.9

**Publication Number:** 0480189

**IPC:** A61K 31/73

**Language of the proceedings:** EN

**Title of invention:**

Pharmaceutical compositions for topical use comprising  
hyaluronic acid sodium salt and disinfectant substances

**Patentee:**

ALTERGON S.A.

**Opponent:**

Prof. Aurelio Romeo

**Headword:**

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**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Inventive step no: obvious to try"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0112/99 - 3.3.2

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.2**  
**of 25 September 2002**

**Appellant:** ALTERGON S.A  
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CH-6900 Lugano (CH)

**Representative:** Gervasi, Gemma, Dr.  
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Corso di Porta Vittoria, 9  
I-20122 Milano (IT)

**Respondent:** Prof. Aurelio Romeo  
(Opponent) Viale Ippocrate 93  
Roma (IT)

**Representative:** Pizzoli, Pasquale Vincenzo  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 3 December 1998  
rejecting the opposition filed against European  
patent No. 0 480 189 pursuant to Article 102(1)  
EPC.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** J. Riolo  
C. Rennie-Smith

## Summary of Facts and Submissions

- I. European Patent No. 0 480 189 based on application No. 91 115 360.9 was granted on the basis of 8 claims.

Independent claim 1 as granted reads as follows:

"Pharmaceutical compositions for topical use comprising hyaluronic acid sodium salt and disinfectant substances chosen from the group consisting of cresol derivatives, hexetidine and sulfadiazine silver salt."

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

The following documents were cited *inter alia* during the proceedings before the Opposition Division and the Board of Appeal:

- (1) US-A-4 736 024
- (4) Remington's Pharmaceutical Sciences, Marck Publishing Company, 16th ed. 1980, page 1108
- (5) Experimental Report conducted by IBSA Institut Biochimique SA
- (6) US-A-4 784 991
- (10) Chemotherapy 14: 195-226, (1969)

Attachment X1 and Attachment X3/2 to the letter of the appellant dated 6 April 2000.

- III. By its decision pronounced on 9 October 1998, the Opposition Division revoked the patent under Article 102(1)EPC for lack of inventive step.

As to novelty, the opponent did not maintain its

objection and the Opposition Division considered that the claimed subject-matter fulfilled the requirement of Article 54 EPC.

The Opposition Division was, however, of the opinion that the subject-matter of the patent in suit did not involve an inventive step.

In that respect, the Opposition Division regarded document (1) as the closest prior art. This document disclosed topical pharmaceutical preparations for, among other things, dermatological applications, containing a pharmacologically active substance - the anti-infective sulfadiazine being mentioned in a list - and hyaluronic acid or a salt thereof - the sodium salt being mentioned in a second list.

The Opposition Division defined the problem to be solved by the contested patent over document (1) as the provision of further topical pharmaceutical compositions comprising hyaluronic acid sodium salt in combination with a disinfectant wherein the components showed compatibility.

It considered that the replacement of sulfadiazine by its silver salt was an obvious alternative which did not involve an inventive step.

In fact, both sulfadiazine and sulfadiazine silver salt were known as bactericides and there was no evidence that these compounds would, *a priori*, not be compatible with hyaluronic acid sodium salt.

Moreover, the synergistic effect shown in the patent in suit could not be considered as unexpected since the

experimental data given in document (1) made it clear that the activity of a drug was enhanced when combined with a hyaluronate. In that respect, it also held that the patentee did not provide any substantial evidence that the pharmacological effect in the eye shown in document (1) would not be repeatable in the skin.

- IV. The appellant (patentee) lodged an appeal against the said decision.
  
- V. Oral proceedings were held before the Board on 25 September 2002.
  
- VI. The appellant argued that, in its view, having regard to the different chemical and pharmacological characteristics of sulfadiazine and silver sulfadiazine, it was not reasonable to consider the replacement of sulfadiazine by its silver salt as an obvious alternative.

In addition, it submitted that it was not correct to assume that the pharmacological effect of a drug in the eye would be repeatable in the skin considering inter alia the completely different structures, types of cells, constituents of the intercellular matrix and blood flow.

It filed additional documentation to demonstrate the different characteristics of sulfadiazine and silver sulfadiazine and the different activity of several compounds mentioned in document (1) when applied to the eyes and to the skin as well as further tests showing the clinical efficacy of the claimed composition and its synergistic properties compared with sulfadiazine (attachment X1).

Finally, it also held that the skilled person would not have considered using hyaluronic acid sodium salt as a vehicle for silver sulfadiazine as there was a technical prejudice against such a combination. To that end, it referred to document (6), to the experimental report (5) and to attachment X3/2.

- VII. The respondent (opponent) submitted that the appellant provided no evidence in support of the technical problem underlying the contested patent, ie "looking for disinfecting components compatible with hyaluronic acid".

It further argued that the synergistic effect demonstrated by the appellant was not valid as it was carried out with *Pseudomonas aeruginosa*, a strain known to be resistant to sulfadiazine as was apparent from document (10).

As to the comparison of the ophthalmological effect and the dermatological effect, it pointed out that the Opposition Division was in fact of the opinion that the synergistic effect shown in document (1) could be fairly expected for all the drugs which were active for a given indication.

Finally, the respondent maintained that the replacement of sulfadiazine by its silver salt was obvious having regard to the fact that the group of sulfadiazines comprised only three members.

- VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained.

The respondent requested that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.
2. *Article 54 EPC*

The opponent did not maintain its novelty objection and the Opposition Division considered that the claimed subject-matter fulfilled the requirement of Article 54 EPC.

The Board sees no reason to depart from the positive conclusion of the Opposition Division as regards the novelty of the claimed subject-matter.

3. *Article 52(1) and 56 EPC*

The only question to be considered in the present decision is therefore whether or not the claimed subject-matter involves an inventive step within the meaning of Articles 52(1) and 56 EPC.

- 3.1.1 Document (1) concerns medicaments for topical use containing various pharmacological substances active or suitable for topical administration such as, among others, anti-infective agents (eg sulfadiazine) and a vehicle comprising hyaluronic acid sodium salt (column 1, lines 11 to 23, column 4, lines 15 to 18, column 6, lines 49 to 54).

Moreover, this document teaches that formulations with hyaluronic acid are advantageous because the hyaluronic acid is a more efficient vehicle for the drugs and

because of the better bioavailability of the active substances as compared to the known pharmaceutical formulations (column 1, lines 34 to 40).

These advantageous effects associated with the use of hyaluronic acid are furthermore confirmed by the pharmacological studies described in the document in column 25, line 64 to column 28, line 46 in relation to various antibiotic and cholinergic agonist drugs (in particular, column 26, lines 43 to 48 and column 28, lines 19 to 24).

Document (4) discloses the use of silver sulfadiazine as an anti-bacterial agent for preventing and treating wound sepsis in patients with burns. The compound is used topically in the form of a cream (page 1108, right column).

The patent is concerned with the problem of topical treatment of infected sores using a pharmaceutical composition comprising hyaluronic sodium salt and disinfectant substances such as sulfadiazine silver salt (page 2, lines 25 to 28).

3.1.2 As discussed during the oral proceedings, in the opinion of the Board document (4), which deals with the problem of topical wound treatment using a disinfectant, represents the closest state of the art (page 1108).

In the light of (4), the problem to be solved appears to be the provision of an improved pharmaceutical formulation of disinfectant substances, including inter alia sulfadiazine silver salt, for the topical treatment of infected sores.



The problem is solved by the pharmaceutical compositions according to claim 1 of the contested patent which comprise hyaluronic acid sodium salt in a formulation of disinfectant substances.

In the light of the working examples disclosed in the patent in suit and the various comparative examples filed during the opposition and appeal procedure, the Board is satisfied that the problem has indeed been solved.

The question to be answered is thus whether the proposed solution would be obvious to the skilled person faced with the problem defined above in the light of the prior art documents.

The Board notes that (1), which also deals with the problem of improving prior art topical medical pharmaceutical formulations containing, inter alia, anti-infective agents (eg sulfadiazine), advocates the use of hyaluronic acid (eg hyaluronic acid sodium salt) as vehicle to that end (see 3.1.1 above).

Moreover, as acknowledged in the description of the prior art in the contested patent, hyaluronic acid was known for its antiphlogistics and stimulating action on the granulation tissue, which accelerates cicatrization and re-epithelialization of lesions.

Accordingly, having regard to these known advantages, the Board is satisfied that the person skilled in the art would have contemplated hyaluronic acid or its derivatives as promising candidates to achieve an improved pharmaceutical formulation of sulfadiazine sodium salt for the topical treatments of wounds.

In view of the above, the Board concludes that the subject-matter of claim 1 does not involve an inventive step.

3.2.1 The Board cannot share the appellant's submissions for the following reasons:

It is not contested that sulfadiazine and silver sulfadiazine have different chemical and pharmaceutical characteristics and that they can therefore not be regarded as obvious alternatives. As is apparent from point 3.1.2 above, these considerations are irrelevant for the assessment of inventive step since the problem to be solved is not the provision of an alternative to sulfadiazine but the provision of an improved formulation containing sulfadiazine silver.

In this respect, the Board acknowledges that the comparative examples filed as attachment X1 show that the efficacy of silver sulfadiazine is enhanced when hyaluronic acid sodium salt is used as a vehicle, whereas the efficacy of sulfadiazine remains unchanged. It is accordingly correct, as argued by the appellant, that the teaching of document (1) that hyaluronic acid as a drug vehicle improves the efficacy of the drug is not as broadly applicable as that document might suggest. The Board is however satisfied that document (1) nevertheless contains a clear incentive, not least because it suggests that the skilled person could easily try a mere mixing of the drug with hyaluronic acid sodium salt. It is noted that the patent says nothing about any particular working conditions or difficulties.

As to the argument that the pharmacological effect of a

drug in the eye would not be repeatable in the skin, the Board notes that the claims of the patent in suit are directed to topical compositions which thus include both ophthalmological and dermatological compositions. The Board observes also that, although the working examples of document (1) relate to ophthalmologic treatments, the teaching of this document concerns medicament for topical use including *expressis verbis* dermatology. There is accordingly no reason to disregard the teaching of document (1).

Concerning the evidence provided by the appellant to demonstrate that the skilled person would have been dissuaded from using hyaluronic acid as a vehicle for sulfadiazine silver because of a technical prejudice in the art against such a combination, the Board observes that, as the case law indicates, a prejudice arises from an opinion or preconceived idea widely or universally held by experts in the field, which is normally demonstrated by reference to the general literature or reference works such as encyclopaedias.

In the present case, the appellant referred to document (6), a US patent, which recites in column 6, lines 4 to 7 that a solution of silver hyaluronate at room temperature and light resulted in gradual browning, development of turbidity and a drop of viscosity within a week or two weeks.

However, in the present case the vehicle is not silver hyaluronate but hyaluronic acid sodium salt. Accordingly, the disclosure in document (6) is not relevant to the present case.

Nor is the disclosure in attachment X3/2 - that silver

sulfadiazine reacts with most heavy metals and that this reaction may result in the release of free silver and darkening of the cream which should then be discarded-sufficient to substantiate the existence of a technical prejudice against the combination of hyaluronic acid sodium salt and silver sulfadiazine since this document, like document (6), is silent about such a combination.

Finally, the Board does not dispute the results of the experimental trials of document (5) demonstrating the incompatibility of the association of hyaluronic acid sodium salt with 6 selected disinfectants. However, the Board considers that these tests *per se* are not sufficient to demonstrate the existence of a technical prejudice in the art as defined above. Moreover, the Board observes that the compounds used in the experiments are not the closest prior art structures to sulfadiazine silver.

Under these circumstances, the Board concludes that the subject-matter of the set of claims as granted does not involve an inventive step as required by Article 56 EPC.

## **Order**

### **For these reasons it is decided:**

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald