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D E C I S I O N
of 21 April 1999

Case Number: T 0425/95 - 3.3.2

Application Number: 88905097.7

Publication Number: 0362270

IPC: A61K 31/565

Language of the proceedings: EN

Title of invention:
Steriod lotion

Patentee:
Schering Corporation

Opponent:
Yamanouchi Europe

Headword:
Topical composition/SCHERING

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes): non-obvious improvement"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0425/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 21 April 1999

Appellant: (Opponent)
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Representative:
-

Respondent: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 9 March 1995 concerning maintenance of the European patent No. 0 362 270 in amended form.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: C. Germinario
R. E. Teschemacher

Summary of Facts and Submissions

I. European Patent No. 0 362 270 was granted in response to European patent application No. 88 905 097.7 on the basis of a set of 11 claims for all the designated Contracting States.

II. Notice of opposition was filed by the appellant, requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step.

The following documents were cited during the proceedings before the opposition division:

(A) Journal American Academy of Dermatology, Vol. 14, pages 79 to 83, (1986);

(C) US-A-3 856 954;

(E) US-A-3 899 580;

(F) Package leaflet for the marketed product: Diprosone^{R} lotion 0.05%;

The document EP-A-0 129 283, which was acknowledged as background art in the description of the opposed patent, was also considered by the parties during the oral proceedings before the Board of appeal.

The opposition division maintained the patent on the basis of an amended set of claims and a description adapted accordingly.

III. The text of claim 1 reads as follows:

"A topical lotion for the treatment of inflammation which comprises 0.01 to 1.0% by weight of the composition of a dermatologically acceptable anti-inflammatory corticosteroid selected from the group consisting of betamethasone 17, 21-dipropionate, alclometasone dipropionate and mometasone furoate in a hydro-alcoholic base comprising:

15 to 50% by weight of propylene glycol;
20 to 40% by weight of isopropyl alcohol;
20 to 60% by weight water;
0.1 to 0.5% by weight of a thickening agent, and sufficient buffer to maintain the pH of the composition within the range of 3.0 to 6.0".

IV. The opposition division held that claim 1, as amended, fulfilled the requirements of Article 123(2) and (3) EPC and that its subject-matter was novel.

In the assessment of the inventive step, the opposition division considered (C) and (E) as the most relevant documents and held that none of the two documents, taken alone or in combination with document (A), disclosed or suggested the improved properties, including high vasoconstrictor activity and excellent anti-inflammatory activity characterising the claimed lotion.

For this reason, the claimed subject-matter was recognised as inventive.

V. The appellant (opponent) lodged an appeal against this

decision. Oral proceedings were held on 21 April 1999.

Having recognised that the subject-matter of the amended claim 1 was novel, the appellant maintained the objection of lack of inventive step.

Although conceding that the compositions according to claim 1 showed some improved vasoconstrictor properties, it contended in writing that this effect was predictable in the light of the teaching in document (E), which disclosed topical compositions of anti-inflammatory corticosteroids in a hydro-alcoholic vehicle comprising all the components of the claimed lotion, ie isopropyl alcohol, propylene glycol, water and thickening agent, and which exhibited maximum skin-penetration properties and maximum therapeutic effect. The only difference recognised by the appellant between the composition of (E) and the lotion of claim 1 was therefore the specific corticosteroids.

In view of the teaching in document (E) and (C), which showed that a hydro-alcoholic base of propylene glycol, isopropyl alcohol and water was particularly suitable for topical compositions of corticosteroids, regardless of the different chemical structure of said active agents, the choice of other more recently developed corticosteroids, whose anti-inflammatory properties made them plainly suitable for the same use, would have been obvious for the skilled person.

During the oral proceedings, the appellant agreed with the Board that the closest prior art was represented by the commercial product "Diprosone^{R} lotion 0.05%", which was cited in document (A) or, in more detail, in

document (F), and which comprised all the elements of the claimed lotion with the exception of propylene glycol.

In the appellant's contentions, the subject-matter of claim 1 lacked inventive step over this commercial composition since the addition of propylene glycol to its base, in order to improve its efficacy, was suggested not only by documents (C) or (E) but also, and specifically, in EP-A-0 129 283.

The appellant also contested the appealed decision since the opposition division, while maintaining the patent in amended form, did not request that the prior documents (C) and (E), on the basis of which the scope of claim 1 had been limited, be acknowledged in the amended description in accordance with Rule 27(1)(b) EPC.

VI. The respondent focused its arguments on the chemical difference between the corticosteroids cited in claim 1 and those described in the prior documents (C) and (E). It specifically emphasised the importance of said difference for the release of the steroids from the topical formulation and for their penetration through the skin, and concluded that the skilled person had no possibility to predict, on the basis of said prior art, the improved vasoconstrictor activity showed by the claimed lotions.

During the oral proceedings, the respondent filed an amended description to acknowledge the newly identified closest prior art, in compliance with Rule 27(1)(b) EPC.

VII. The appellant (opponent) requested that the decision under appeal be set aside and European patent No. 0 362 270 be revoked (main request); in case the patent were maintained, it requested that the description be amended in order to acknowledge the closest prior art (auxiliary request).

The respondent (patentee) requested that the appeal be dismissed and the patent be maintained in the version as submitted during the oral proceedings before the Board.

Reasons for the Decision

1. The appeal is admissible.

2. The compliance of claim 1 as amended in the first instance with the requirements of Article 123(2) and (3) EPC and the novelty of the claimed subject matter were recognised by the opposition division without being contended by the appellant. The Board shares this opinion. In fact, the specific anti-inflammatory corticosteroids now cited in claim 1 are disclosed in claims 4, 7 and 9 as originally filed. Since no cited prior document describes a topical lotion comprising the same components in the same amounts, the novelty of amended claim 1, and of dependent claims 2 to 8 is recognised by the Board.

3. *Inventive step*

3.1 Both documents (C) and (E), taken alone, have been discussed during the proceedings as suitable starting

documents for assessing the inventive step of the claimed subject-matter.

The Board does not share the view that either of the two documents represents the closest prior art. In fact, though both describe topical compositions comprising anti-inflammatory corticosteroids, these differ in many respects from the lotions of claim 1.

More particularly, document (E) discloses topical gels, comprising a higher amount of thickening agent, ie 2.6% (see claim 1), a higher amount of propylene glycol, ie about 54-84% (see claim 1 and examples 1 to 6), a lower amount of water, ie 8-18% (see claim 1) and, more importantly, corticosteroids, which are different to those of present claim 1.

Like the former, document (C) describes topical compositions in the form of a gel, comprising, according to the examples, a higher amount of thickening agent, ie more than 1.0% and different anti-inflammatory corticosteroids. Moreover, the stated purpose of this invention is not that of improving the efficacy of the medicament, but simply that of providing a suitable and stable topical composition (column 1, lines 8 to 25).

On the other hand, the Board also wishes to consider the commercial product named "DIPROSONE^{R} Lotion 0,05%" described in document (F). This product is a lotion comprising betamethasone 17, 21 dipropionate (0,64 mg/g composition), in a vehicle consisting of isopropyl alcohol (45%) and purified water slightly thickened with Carbomer 934P. This composition shares, of all the

prior compositions cited, the highest number of essential features with the claimed lotion, the single relevant point of difference being the lack of propylene glycol. Although no publication date is reported in this document, the same commercial product named "DIPROSONE^{R} Lotion" is cited in document (A), page 82 and 83, which is dated January 1986. For this reason, the Board is of the view that this commercial product belongs to the state of the art pursuant to Article 54(2) EPC and that it represents the closest prior art.

3.2 The problem to be solved by the invention, defined in relation to document (F), is that of providing topical compositions of the claimed corticosteroids exhibiting improved percutaneous adsorption of the specific steroids.

The solution proposed by the patent according to present claim 1 is a lotion in which a defined amount of propylene glycol has been added to the hydro-alcoholic vehicle of a lotion such as the one described in document (F).

The patent contains comparative tests, the results of which, illustrated in tables I to IV, prove that lotions comprising propylene glycol exhibit a higher vasoconstrictor activity as compared to lotions free of propylene glycol or comprising other glycols. As explained in the patent (page 6, lines 22 to 23), and as confirmed in the McKenzie et al. article (Arch. Dermatol., 86, 608 (1962)) produced in the original during the appeal proceedings, vasoconstriction, tested according to the McKenzie's assay, is recognised among

experts in the field as an index of the percutaneous absorption of steroids.

Therefore, the Board accepts that the higher vasoconstrictor score illustrated in tables I to IV reflects the improved percutaneous adsorption characterising the claimed lotions. For this reason, the Board is satisfied that the underlying technical problem has been solved by the present invention.

3.3 In assessing the inventive step involved in the claimed subject-matter, the Board wishes firstly to stress that the closest prior art, document (F) is a simple package leaflet intended to inform the patient, in a neutral way, of the content, use, and main and secondary effects of the commercial product DIPROSONE Lotion. Therefore, this document in itself cannot direct the skilled person to the solution of the technical problem proposed by the present invention.

3.4 On the other hand, it was argued during the oral proceedings that the skilled person, faced with the problem to be solved, would have found a clear suggestion of the solution proposed by the patent in suit in the prior document EP-A-0 129 283, which reported, on page 5, lines 29 to 32, that **propylene glycol had been described in several articles in the literature as enhancing the penetration of certain pharmacologically active agents, such as corticosteroids**.

This sentence is not directly related to the invention representing the subject-matter of the aforementioned EP application, but it is a statement allegedly

reflecting the prior art knowledge inferred from the pieces of literature cited immediately thereafter. However, the appellant, who relied on this specific passage and on whom the burden of proof rested, did not provide the Board with any of these original prior documents. Under these circumstances, the relevance of this statement can only be recognised by the Board if confirmed or made plausible by the whole technical content of the prior EP application.

The document describes penetration-enhancing pharmaceutical compositions for topical application comprising a corticosteroid and a solvent, such as water, ethanol or 2-propanol (ie isopropanol). As penetration-enhancing agent, the compositions further contain a diol, such as 1,2-propanediol (ie propylene glycol), 1,2-, or 1,3-, or 2,3-butanediol and a cell-envelope disordering compound, such as methyl laurate, oleic acid, oleyl alcohol etc. The penetration-enhancing effect of the different agents is tested and compared in examples 1 to 31, the amounts, in micrograms, of corticosteroid penetrated into the diffusion cell being scored alongside each composition. The results show unambiguously that the penetration of triamcinolone or hydrocortisone caused by propylene glycol alone or by the mixture propylene glycol/ethanol is dramatically lower than the effect obtained with any of the penetration-enhancing systems of the earlier EP application. These results alone cast serious doubt on the penetration-increasing effect of propylene glycol as envisaged in the sentence on page 5. Moreover, examples 28, 29 and 30 show that the alleged "enhancing effect" of propylene glycol is even lower than that of pyrrolidine or derivatives thereof which replace

propylene glycol in some compositions and which are not even quoted in this document as possible penetration-enhancing agents. Under these circumstances, the Board's judgment is that the statement indicated by the appellant, not only is not confirmed or made believable, but is contradicted by the technical teaching in EP-A-0 129 283. For these reasons, the skilled person would not have found in the earlier EP-A-0 129 283 any reliable suggestion of the same solution of the technical problem proposed by the patent in suit.

3.5 Documents (A) (C) and (E) have also been discussed by the appellant during the appeal proceedings as relevant prior art.

Document (C) describes topical steroid compositions in the form of a gel, comprising, as excipient, propylene glycol, isopropyl- or ethyl-alcohol, and a thickening agent. The properties sought for these compositions are the simple ability to bring the active substance to the application site and to release it for absorption - which, in the Board's view, is the minimum requirement for a topical composition - and stability.

This document is not concerned with the problem of the skin penetration of the active agent and for this reason it fails to recognise or at least to envisage the possibility that propylene glycol may improve the adsorption of anti-inflammatory steroids. Therefore, the skilled person would not have found in this prior art any reasonable motivation to consider the propylene glycol as an adsorption enhancer at all, and still less as an enhancer for the specific corticosteroids of

claim 1 of the patent in suit.

3.6 The skilled person could not find any more efficacious assistance in document (A), which is a simple list of most of the current topical corticosteroid preparations commercially available in the USA in 1986. From this document the skilled reader could only derive that propylene glycol was, among many others, a suitable component for topical compositions. However, no hint of its effect as a skin penetration enhancer for specific steroids could be inferred from it.

3.7 Unlike the former documents, document (E) describes anti-inflammatory corticosteroid compositions exhibiting maximum skin penetration and high therapeutic efficacy. However, many differences exist between these prior compositions and the claimed lotions, specifically the higher amount of propylene glycol, the higher amount of water, the gel form, and the different anti-inflammatory corticosteroids.

In any attempt to give a solution to the technical problem, the skilled person would have considered the excipient disclosed in (E), ie propylene glycol, isopropanol and water, only if he could reasonably foresee in it a valid solution for said problem.

As emphasised by the respondent and accepted by the Board, the development of the therapeutic effect upon topical administration of a medicament is the result of a multi-step process comprising the release of the active agent from the excipient, the absorption of the substance into the skin and the interaction of the adsorbed substance with the cell functions. It is well known to the skilled person that this process is not independent of the chemical nature of the active substance, specifically of its hydrophilic - hydrophobic properties, to the extent that a significant modification of these properties may strongly change or impair the penetration characteristics and the activity of the substance. According to document (E), the mixture isopropyl alcohol/propylene glycol is able to give maximum skin penetration to corticosteroids which are not only in themselves different from the steroids of the patent in suit, but, more importantly, are all in the form of free alcohol, as specified in claim 1 of that document. Therefore, relying on the teaching in (E), the skilled person had no possibility to predict any desirable, positive effect on the penetration properties of the corticosteroids of claim 1 of the patent in suit, which are all in the form of esters.

If, nevertheless, the skilled person had envisaged the addition of propylene glycol, as taught in (E), to the lotion according to the closest prior art, document (F), he would not have found in this prior document any reason for using the glycol in an amount falling outside the range indicated in (E), ie 54 to 84%, namely to decrease this amount below the value 50% as required by claim 1 according to the patent in suit. In

fact, the reduction of the glycol could obviously affect the desired penetration properties of the composition.

In conclusion, none of the cited prior documents (A), (C) or (E) suggests to the skilled person that propylene glycol should be added, in the claimed amount, to the hydro-alcoholic lotion of document (F), in order to improve the skin penetration of the anti-inflammatory corticosteroid of claim 1.

In view of the foregoing, the Board judges that the subject-matter of claim 1, and accordingly of dependent claims 2 to 8 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent as amended in the following version:

Description: pages 1, 1a, 2 to 6,

Claims: 1 to 8,

both submitted during the oral proceedings on 21 April 1999.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon