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D E C I S I O N
of 15 November 2000

Case Number: T 0396/97 - 3.3.2

Application Number: 87902908.0

Publication Number: 0305380

IPC: A61K 31/78

Language of the proceedings: EN

Title of invention:
Novel topical metronidazole formulations

Patentee:
GALDERMA S.A.

Opponent:
Dr. August Wolff Chemisch Pharmazeutische Fabrik GmbH & CoKG

Headword:
Topical metronidazole/GALDERMA

Relevant legal provisions:
EPC Art. 52(4), 54, 56, 123

Keyword:
"Main request and auxiliary requests 1 and 2 - inventive step no - obvious alternative composition"
"Auxiliary request 3 - not admissible - treatment of human body"
"Fourth auxiliary request - not admitted into the proceedings - filed at the very end of the oral proceedings and total shifting of the invention - abuse of procedure - yes"

Decisions cited:
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Catchword:

-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0396/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 15 November 2000

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 16 January 1997 concerning maintenance of European patent No. 0 305 380 in amended form.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
M. B. Günzel

Summary of Facts and Submissions

I. European patent No. 305 380, based on international application No. PCT/US87/00584, was granted on the basis of 20 claims.

II. An opposition was filed against the granted patent by the Appellant (Opponent) alleging lack of novelty and lack of inventive step under Article 100(a) EPC.

During the proceedings the following documents were inter alia cited:

(1): RO-A 80363 and its English translation

(2): RO-A 91013 and its English translation

(3): B. Mollgaard et al., "Vehicle effect on topical drug delivery", Acta Pharm. Suec. 20, 443-450 (1983)

(4): FR-A-2 558 058

III. By its interlocutory decision dated 16 January 1997 the Opposition Division maintained the patent pursuant to Article 102(3) EPC on the basis of an amended set of claims 1 to 18 received on 18 July 1996, of which the sole independent claim reads:

"1. A dermatological preparation for topical application in the form of an aqueous gel composition consisting essentially of
(a) a therapeutically effective amount of metronidazole in a concentration of from 0.25% to 1% by weight as the sole therapeutically active ingredient,

(b) a polycarboxylated vinyl polymer in an amount effective to promote solubility of the metronidazole and to cause gelling of the composition,
(c) an aqueous solvent, and
(d) from 2% to 5% by weight of a penetration enhancer, wherein the preparation is substantially free of comedogenic, acneogenic, irritating and skin drying ingredients."

The Opposition Division noted that the novelty of the subject-matter of the claims was not contested by the Opponent and held that the requirements of Article 54 EPC were fulfilled.

As regards inventive step the Opposition Division considered document (1) in the form of its English translation as the closest prior art. The essential differences between the claimed compositions and those of document (1) were the amount of metronidazole and the fact that metronidazole was the sole therapeutic active compound in the claimed compositions.

In the Opposition Division's view there was a further difference in the use of the compositions, namely for the treatment of skin disorders according to the patent in suit instead of vaginal disorders referred to in document (1).

Since the problem underlying the patent in suit was the provision of a dermatological metronidazole preparation which avoided the drawbacks of the previously known compositions, and since the prior art documents related to different problems, there was no incentive to combine the other prior art documents with the closest prior art and an inventive step was acknowledged.

IV. The Appellant (Opponent) lodged an appeal against this decision.

V. Oral proceedings took place on 15 November 2000. At the very end of the oral proceedings the Respondent submitted four auxiliary requests.

VI. The Appellant's submissions in written form and during the oral proceedings may be summarised as follows:

Document (4) represented the closest prior art. The only technical features of the claimed compositions which were not directly derivable from document (4) were the use of a polycarboxylated vinyl polymer as gelling agent and the amount of penetration enhancer. In the absence of any advantage or improvement, the only problem to be solved by the patent was the provision of an alternative dermatological composition containing metronidazole suitable for the treatment of acne.

Gels containing metronidazole as active ingredient, carbopol as gelling agent and propylene glycol as penetration enhancer were known from documents (1) and (2). Although these documents related to compositions used for the treatment of vulvovaginitis, the person skilled in the art, who in the present case was a pharmacist specialised in formulations, would consider the teaching of these documents since they disclosed preparations containing the same active ingredient as in the patent in suit.

Moreover, it was self-evident that dermatological compositions should be free of comedogenic, acneogenic, irritating and skin-drying ingredients.

Concerning the fact that document (4) put emphasis on compositions containing in addition to metronidazole a keratolytic active ingredient, the Appellant mentioned that the activity which could be attributed to this additional compound in document (4) was not demonstrated for the claimed compositions since the examples of the patent in suit showed only an effect on inflammation.

Consequently, the teaching of document (4) in combination with those of documents (1) and/or (2) led directly to the subject-matter of the patent in suit.

VII. The Respondent also considered document (4) as the closest prior art and took the view that the claimed compositions represented alternatives compared with the compositions disclosed in this prior art.

Document (4), however, taught away from the present invention as it indicated the use of metronidazole in combination with at least one keratolytic agent in order to treat the epidermal, the infectious and the inflammatory aspects of acne.

Moreover, there was no teaching in document (4) as to the selection of the specific vehicle of the present invention, thereby reducing the number of required active ingredients.

The skilled person was clearly not the pharmacist specialised in formulations but the medical doctor specialised in dermatology who would consequently not consider the teaching of documents (1) and (2) which related to gynaecology, a totally different medical field.

VIII. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

As a main request the Respondent requested that the appeal be dismissed. As auxiliary requests the Respondent requested that the decision under appeal be set aside and the patent be maintained with the claims of any of auxiliary requests 1 to 4, taken in their consecutive order.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Neither the Appellant nor the Opposition Division raised objections under Article 123(2) and (3) EPC and the Board for its part, sees no formal objections to the set of claims forming the basis of this request.

3. Novelty of the subject-matter of the claims was acknowledged by the Opposition Division. The Appellant did not raise an objection under Article 54 EPC regarding the subject-matter of the main request and the Board also sees no reason to question the novelty of the claimed compositions.

4. In the Board's view document (4) represents the closest prior art.

4.1 Document (4) relates to dermatological compositions for topical application for the treatment of acne, avoiding in particular the drawbacks of the oral administration

of metronidazole. The compositions according to this prior art contain 0.1 to 5% metronidazole in association with at least one keratolytic active agent selected from benzoyl peroxide and vitamin A acid and its derivatives, and a support providing the penetration and the remanence of the active ingredients in the skin. The preferred support is a mixture of ethanol and polyethylenglycol (see in particular claim 1 as well as page 3, lines 14 to 22 and page 7, lines 19 to 21).

According to document (4), the components of the composition have an effect on different aspects of acne syndromes and symptoms respectively, namely by the presence of metronidazole on the inflammatory and infectious part and also by the presence of the keratolytic agent on the epidermic part of the disease. The compositions are described as suitable for the treatment of all types of acneic lesions. Furthermore, the active ingredients are well tolerated and the compositions are less irritating (see in particular page 6, lines 7 to 24). Document (4) mentions also the possibility of using metronidazole alone and indicates that in such a case only the inflammatory and infectious aspects of acne will be overcome (see in particular page 5, lines 4/5).

The possibility of using metronidazole in the form of gel is indicated in document (4), among other possibilities, as for example, creams or solutions (see in particular page 8, lines 1 to 7).

4.2 By reference to experimental data set out in the description of the patent in suit, the Respondent has alleged an improvement of the dermatological

preparation of the patent in suit over known preparations for topical application in the form of an aqueous gel. However, the data presented in the patent in suit only show effects obtainable with gel compositions when compared to placebo compositions.

In the absence of other experimental data or any other evidence clearly allowing a **direct comparison** of medical, chemical or any technical effects obtainable by the preparations of the patent in suit with those obtainable by preparations known from document (4).

The problem underlying the patent in suit can only be seen in the provision of alternative compositions for topical treatment of skin diseases, in particular acne.

The claimed solution to this problem is the dermatological preparation in the form of an aqueous gel according to claim 1 consisting of metronidazole as the sole therapeutically active agent in combination with a polycarboxylated vinyl polymer and from 2% to 5% by weight of a penetration enhancer.

Having regard to the worked examples of the patent in suit, the Board is convinced that the problem of providing alternative compositions for topical treatment of skin deseases has indeed been solved. This was not contested by the parties.

4.3 However, the question remains whether in the light of the prior art the claimed solution was obvious to the skilled person.

Document (4) does not explicitly mention that the compositions are substantially free of comedogenic,

acneogenic, irritating and skin-drying ingredients. However, as argued by the Appellant, it must be self-evident to a person skilled in the art that a composition applied to the skin in order to treat acne should be free of ingredients inducing other skin diseases and undesired effects on the skin and no arguments to the contrary have been presented. In this respect, it is to be noted that document (4) clearly describes products as being well-tolerated and less irritating.

Furthermore, document (4) mentions the possibility of using metronidazole alone and indicates that in such a case only the inflammatory and infectious aspects of acne will be overcome. Accordingly, the Board cannot follow the Respondent's argument that document (4) only teaches that metronidazole must be used in association with a keratolytic agent.

It appears plausible, as argued by the Respondent, that the composition of document (4) contains a keratolytic agent in order to obtain an epidermic effect which results, in particular, in a shorter period of treatment. However, in the absence of any evidence on file that the epidermic effect **and** a shorter treatment can also be obtained by the use of the compositions of the patent in suit, the Board can only conclude that the patent in suit follows the obvious teaching of document (4), namely the possibility of using metronidazole whilst abandoning the effect linked to the keratolytic agent.

As argued by the Respondent, there is indeed no suggestion in document (4) that a composition in the form of a gel be specifically used or that preference

be given to it, other possibilities being thus equally envisaged.

However, it was known to the skilled person from document (3) that metronidazole, when incorporated in gels, and in particular aqueous carbopol gels, is properly transported through the skin when associated with propylenglycol. Figure 4 on page 449 of this document shows an almost 100 percent penetration of metronidazole through human skin *in vitro,* after 90 hours.

Consequently, the disclosure of document (3) provides a major incentive for the skilled person to try first, among the other possibilities offered in the closest prior art, carbopol gels in association with penetration enhancers, in particular because this type of formulation has already been recognised in the art as an adequate vehicle for metronidazole.

Documents (3) and (4) do not disclose concrete gel preparations. However, once there is an incentive to try to prepare gels as suggested in documents (3) and (4) for the treatment of acne, the skilled person would, regardless of the actual disease to be treated, consider other documents relating to such gel preparations containing metronidazole.

The skilled person would consequently consider documents (1) and (2) which relate to gels containing metronidazole (see (1), examples 1 to 3 as well as the claim and (2), examples 1 to 3 as well as the claim).

These documents showed that metronidazole can be formulated as aqueous gels in the presence of water and

carbopol 940 (see the worked examples of both documents), which is also the preferred polycarboxylated vinyl polymer according to the patent in suit. Penetration enhancers were also incorporated in the gels. In particular, example 1 of document (1) discloses the use of propylenglycol, a preferred penetration enhancer according to the patent in suit, in the same amount as specified for the presently claimed compositions.

Accordingly, the skilled person could clearly derive from document (1) or (2) each of the ingredients in combination permitting a formulation of metronidazole in the form of a gel.

Although these documents concern vaginal gels which are intended to be used on mucous membranes, document (2) explicitly mentions that these gels are likewise capable of penetrating at the cutaneous membrane level (see page 4, lines 4/5), and document (3), as indicated above, shows clearly that this type of gel is an adequate vehicle for metronidazole delivery through the skin.

Accordingly, the skilled person, when combining the teaching of documents (4) and (3) with the teaching of document (1) or (2), would solve the problem defined above without the exercise of inventive skill and consequently would arrive in an obvious way at the preparations of the patent in suit.

The Respondent's counter-arguments are mainly based on the view that the skilled person faced with the present invention is a medical doctor specialising in dermatology. For this reason the skilled person would

not consider documents which are not related to dermatology and would therefore disregard documents (1) and (2) as they relate to gynaecology.

The Board cannot share this opinion for the following reasons. The starting point for deciding who is the appropriate skilled person is the objective technical problem to be solved. The skilled person is therefore not necessarily the person who will make use of the final invention.

Indeed, taking account of the differences between the presently claimed alternative and that of the closest prior art, it is clear that the claimed solution to the problem underlying the patent in suit is related to using an adequate support and vehicle for metronidazole delivery and thus to specific knowledge of preparation procedures of galenic formulations. The person who will have to solve this problem and who is the most adequately skilled to do this is, as mentioned above, a pharmacist specialised in formulating compositions for topical use and not the dermatologist, who will make use of the formulation by prescribing it to patients suffering from acne, and who will not necessarily be skilled in pharmaceutical formulations.

Accordingly, the Board can only conclude that to the relevant person skilled in the art the dermatological preparation of claim 1 of the main request represented an obvious alternative to those already known from document (4).

The subject-matter of claim 1 of the main request therefore does not fulfil the requirements of Article 56 EPC.

Auxiliary requests 1 to 3

5. The Respondent did not dispute that the claims according to auxiliary requests 1 and 2 contain only "cosmetic" modifications which can therefore not alter the Board's assessment of inventive step as compared with the claims of the main request.

Auxiliary request 3 is clearly not allowable as it comprises a claim directed to a method for treatment of the human body by therapy (Art. 52(4) EPC). This was ultimately not contested by the Respondent.

Auxiliary request 4

6. Auxiliary request 4 was only submitted by the Respondent at the very end of the oral proceedings before the Board. The Board refuses this request because its filing at that stage constitutes an abuse of proceedings.

6.1 By contrast with the subject-matter of the Respondent's main, first and second auxiliary requests which were all directed to - limited - definitions of the granted dermatological preparations, the Respondent sought by auxiliary request 4 to introduce claims directed to the use of the composition for the preparation of a pharmaceutical composition for the treatment of rosacea.

As has been set out above under 4.2, the technical problem to be solved in relation to the state of the art by the invention as claimed previously was not that of providing a composition for the treatment of rosacea but that of providing an - alternative - dermatological

composition for the topical administration of metronidazole, the claimed solution consisting in providing in the composition a suitable support and vehicle for the transport of metronidazole through the epidermis by the use of a specific gelling agent and a defined amount of penetration enhancer in the claimed compositions. It is immediately evident that, compared with this technical problem and its solution, the subject-matter claimed by auxiliary request 4 would have significantly changed the nature of the claimed invention. Indeed, as set out under point 4 above, the dermatological preparation as claimed according to the main request is obvious to a person skilled in the art and the Respondent had never previously alleged that such preparations had an improved therapeutical effect on rosacea compared with the compositions known from the prior art and no data were filed showing any such effect. Admitting auxiliary request 4 into the proceedings would therefore have required new submissions by the parties, including at least further data from the Respondent and possibly an additional search to be made by the Appellant, followed by a complete reconsideration of the case by the Board. This would have entailed either the continuation of the proceedings before the Board in writing or remittal of the case to the Opposition Division for further prosecution.

6.2 The reasons which may have prompted auxiliary request 4 were, however, known to the Respondent from the beginning of the appeal proceedings, indeed even at the opposition stage. Up to the date set for oral proceedings before the Board the Respondent had more than eight years time from the filing of the opposition to consider appropriate "fall-back positions" for

defending the patent in response to the Appellant's arguments. As appears from the jurisprudence of the Boards of Appeal, one important reason why the filing of auxiliary requests is allowed is to ensure that "fall-back" requests are filed in time and do not unduly prolong the proceedings.

6.3 Moreover, at the beginning of the oral proceedings before the present Board, after having read out the request of the parties, the chairman had asked the parties to confirm whether or not they stood by their requests filed in writing. This was confrimed by both parties.

6.4 In these circumstances the Board considers it an abuse of proceedings that the Respondent nevertheless waited until the very end of the oral proceedings to suddenly file auxiliary request 4 changing the nature of the subject-matter claimed to a very substantial extent.

Respondent's auxiliary request 4 had therefore to be refused.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Townend P. A. M. Lançon