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**Datasheet for the decision
of 26 November 2018**

Case Number: T 0932/16 - 3.3.07

Application Number: 08462004.6

Publication Number: 2149375

IPC: A61K33/06, A61K33/12, A61P17/00

Language of the proceedings: EN

Title of invention:
Compositions for the treatment of dermatological diseases, and
uses thereof

Applicant:
Despharma Kft.

Headword:
Compositions for the treatment of dermatological diseases, and
uses thereof/Despharma Kft.

Relevant legal provisions:
EPC Art. 56

Keyword:
Request for video conference (No)
Request for postponement of oral proceedings (No)
Inventive step - All requests (No)

Decisions cited:

Catchword:



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Chambres de recours

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Case Number: T 0932/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 November 2018

Appellant: Despharma Kft.
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Pagony u. 50 (HU)

Representative: Brantsandpatents bvba
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 3 December 2015
refusing European patent application No.
08462004.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
P. Schmitz

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application n°08462004.6. The decision was based on 4 sets of claims, namely the main request and auxiliary requests 1-2 filed with letter of 13 October 2015 and auxiliary request 3 filed during the oral proceedings of 13 November 2015.

Claim 1 of the main request read as follows:

"1. A topical composition comprising

a) clinoptilolite;

b) a physiologically acceptable magnesium salt;

c) water; and

d) a substantially non-cationic carrier;

wherein the molar amount of magnesium ions is higher than the molar amount of calcium ions."

II. The documents cited during the examination proceedings included the following:

D3: WO 2006/108414

D7: Denda Mitsuhiro et al., Archives of Dermatological Research, 291, 10, October 1999, p. 560-563

D11: Christoph M. Schempp et al., J. of Inv.

Dermatology, 115, 4, October 2000, p. 680-686

D12: Grzesiak John et al., J. of Clin. Invest., 95, 11995, p. 227-233

III. According to the decision under appeal, D3 disclosed the topical use of zeolite, such as clinoptilolite for the treatment of psoriasis (see examples), and suggested the addition of magnesium or calcium salts. D3 represented the closest prior art. The subject-matter of claim 1 of the main request differed in that the presence of magnesium was required. The problem was

seen in the provision of an alternative composition or to select from the two suggested options (addition of Mg or Ca salts) the option with better therapeutic activity. In order to solve the underlying problem, the person skilled in the art would have searched for agents that have a positive effect on skin barrier function. The skilled person knew from D7 that higher Mg levels promoted skin recovery faster than high Ca levels; D11 and D12 disclosed the positive effect of Mg on psoriasis, atrophic dermatitis and wound healing. The person skilled in the art would therefore have known that an excess of magnesium was essential, and would have selected a composition with higher amounts of Mg. Consequently, the subject-matter of claim 1 of the main request did not involve an inventive step.

The first and second auxiliary requests were not inventive for the same reasons as the main request.

Auxiliary request 3 did not meet the requirements of Article 123(2) EPC and was also not inventive, since no effect had been shown for a limitation of the amounts of water and Mg.

IV. The applicant (hereinafter the appellant) filed an appeal against the decision of the examining division. With the statement setting out the grounds of appeal dated 3 April 2016, the applicant filed a main request and auxiliary requests I-V. It also submitted the following pieces of evidence:

Annex 1: Feleki Report

Annex 2: Epidemal barrier rescue report

Claim 1 of the main request read as follows as is identical with the main request underlying the appealed decision:

"1. A topical composition comprising
a) clinoptilolite;
b) a physiologically acceptable magnesium salt;
c) water; and
d) a substantially non-cationic carrier;
wherein the molar amount of magnesium ions is higher
than the molar amount of calcium ions."

Claim 1 of auxiliary request I was amended by the
feature "and whereby said composition has a negative
zeta potential and is able to form an electric double
layer in an aqueous medium".

Claim 1 of auxiliary request 2 read as follows, the
difference with respect to the main request being
indicated in **bold**:

"1. A topical composition comprising
a) clinoptilolite;
b) **between 0.2 and 30w/w% of magnesium chloride
hexahydrate;**
c) **between 30 and 80 w/w% of** water; and
d) a substantially non-cationic carrier;
wherein the molar amount of magnesium ions is higher
than the molar amount of calcium ions **and whereby said
composition has a negative zeta potential and is able
to form an electric double layer in an aqueous medium.**"

Claim 1 of auxiliary request 3 read as follows, the
difference with respect to the main request being
indicated in **bold**:

"1. topical composition comprising
a) clinoptilolite;
b) a physiologically acceptable magnesium salt;
c) water; and
d) a substantially non-cationic carrier;

wherein the molar amount of magnesium ions is higher than the molar amount of calcium ions **for use in the formation and/or recovery of the epidermal barrier function in patients affected by an inflammatory disease or condition.**"

Claim 1 of auxiliary request 4 read as follows, the difference with respect to the main request being indicated in **bold**:

"1. topical composition comprising
a) clinoptilolite;
b) **between 0.2 and 30w/w% of magnesium chloride hexahydrate;**
c) **between 30 and 80 w/w% of water;** and
d) a substantially non-cationic carrier;
wherein the molar amount of magnesium ions is higher than the molar amount of calcium ions **for use in the formation and/or recovery of the epidermal barrier function in patients affected by an inflammatory disease or condition.**"

Claim 1 of auxiliary request 5 read as follows, the difference with respect to the main request being indicated in **bold**:

"1. topical composition comprising
a) clinoptilolite;
b) **between 0.2 and 30w/w% of magnesium chloride hexahydrate;**
c) **between 30 and 80 w/w% of water;** and
d) a substantially non-cationic carrier;
wherein the molar amount of magnesium ions is higher than the molar amount of calcium ions and **whereby said composition has a negative zeta potential and is able to form an electric double layer for use in the formation and/or recovery of the epidermal barrier**

function in patients affected by an inflammatory disease or condition."

- V. Summons to oral proceedings scheduled for 26 November 2018 were sent to the appellant on 9 April 2018.
- VI. A communication dated 16 October 2018 expressing the board's preliminary opinion was sent to the appellant. The Board's opinion was that none of the requests seemed to be inventive over D3.
- VII. With the letter dated 22 October 2018, the appellant requested that oral proceedings be arranged in the form of a video conference.
- VIII. The Board informed the appellant by a communication dated 26 October 2018 that video conferences were not foreseen before the Boards of Appeal and that there was no established procedure as to this regard yet. Accordingly, the request was not allowed.
- IX. With a letter dated 5 November 2018, the appellant requested postponement of the oral proceedings in view of oral proceedings scheduled for another case on 26 November 2018 at the EPO and for proceedings before the Court of Brussels scheduled for 27 November 2018.
- X. With its communication dated 9 November 2018, sent by fax on 6 November 2018, the Board informed the appellant that it could not grant a postponement of the oral proceedings.
- XI. With a letter dated 8 November 2018, the appellant informed the Board that it will not be in the capacity

of attending the scheduled oral proceedings and requested to continue the proceedings in writing.

XII. Oral proceedings before the Board of appeal took place on 26 November 2018 in the absence of the appellant.

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

Main request - Inventive step

D3 could be seen as the closest prior art for the current invention. D3 described an agent comprising a zeolite and calcium and/or magnesium salts. Clinoptilolite was mentioned as a possible zeolite. Dolomite was given as potential source for calcium and magnesium. The agent according to D3 could be useful for skin diseases such as psoriasis.

D3 did not describe the presence of substantially non-cationic carrier, nor did it describe that the molar amount of magnesium ions should be higher than the molar amount of calcium ions. D3 was also not enabled for a topical cream comprising clinoptilolite and specific ratio between magnesium and calcium ions. D3 did indeed not provide any sufficient instructions to a skilled person to believe that the oral composition of D3 was efficient when applied topically.

The technical effect achieved from the solution given by the current invention was thus the provision of an optimally working topically applicable composition. It was the specific synergistic interplay of the various ingredients of the current composition which resulted in a positive effect on the epidermal barrier. The inventors of the current invention had surprisingly

found that the combination of a negatively charged clinoptilolite and specific balance between magnesium and calcium ions had a positive effect on this epidermal barrier, whereby the effect surpasses that of the mere sum of the individual components. In fact, both the clay material as well the well-defined balance between magnesium and calcium exerted a synergistic effect on the establishment and/or the recovery of the epidermal barrier.

This synergistic effect was supported by the experimental data Annex I. Four compositions were used in which the third composition was a composition according to the current invention (clinoptilolite + excess of Mg vs Ca ions). The graph on page 3 of the report illustrated the results. From the results, it was obvious that composition 3 behaved superior in view of the other compositions.

Annex 2 was an additional experimental report, performed by the appellant, which further supported the synergistic effect of clinoptilolite and a molar excess of magnesium. In an in vitro skin model, penetration of luciferin yellow through the stratum corneum was visualised. When the epidermal barrier is intact, such penetration was inhibited. Addition of a solution comprising zeolite, and a molar excess of magnesium (compared to calcium) as well as addition of a commercial cream according to the current invention (Dermalex®) resulted in an almost complete rescue of the barrier, comparable to the controls. From the results, it was obvious that a combination of zeolite and magnesium resulted in a barrier repair which surpasses the activity of the two ingredients alone.

A skilled person, looking for an optimisation of the composition in D3 should have been, based on the teachings in D7, rather be inclined to favour equimolar concentrations of magnesium and calcium ions.

The claimed composition was therefore inventive.

Auxiliary request I - Inventive step

The presence of a zeta potential and the formation of a electric double layer was not disclosed in D3.

Auxiliary request II - Inventive step

The claimed concentrations were crucial for the repair or formation of the epidermal barrier.

Auxiliary request III-V - Inventive step

D3 was silent about the specific use claimed in these requests.

XIV. Requests

Appellant (applicant) requested that the decision under appeal be set aside and a patent be granted on the basis of the sets of claims of the main request or one of auxiliary requests I-V, all filed with the statement setting out the grounds of appeal of 3 April 2016.

Reasons for the Decision

1. Procedural issues

1.1 Request that oral proceedings be arranged in the form of a video conference

The holding of oral proceedings as a videoconference is either foreseen in the EPC, nor in the RPBA. The Board has therefore a discretion whether or not to allow oral proceedings in this form. This discretion is exercised according to the circumstances in any given case, including whether the case at hand is ex parte or inter partes, and is dependent on the complexity of the file. A further important issue is the availability of suitable rooms for oral proceedings before the board by video conference. This would typically require that provision also be made for the public (cf. T 2068/14 dated 30 July 2015).

At present, video conference facilities are not foreseen for the Boards of Appeal in the Haar buildings and there is no established procedure as to this regard yet.

Consequently, the Board could not allow the request to hold the oral proceedings by video conference.

1.2 Request for postponement of the oral proceedings

With its letter dated 5 November 2018, the appellant's representative requested the postponement of the oral proceedings before the Board scheduled for 26 November 2018, because he had oral proceedings scheduled for 26 November 2018 at the EPO in Rijswijk for case EP 2 844 6692 and the supporting attorney on this file had proceedings before the Court of Brussels on 27 November 2018.

The Board could not grant this request for following reasons.

First, the request was filed very shortly before the oral proceedings before the Board while the appellant was already summoned on 9 April 2018. If said request had been filed early after the summons, setting the date of oral proceedings on another date in 2018 would have been possible.

The Board had also to take in account its heavy workload and its tight schedule; a postponement of the oral proceedings planned for 26 November 2018 at such late stage would have delayed the holding of the oral proceedings to late 2019 or 2020.

Moreover, the Board notes that the invitation to the oral proceedings for the case in Rijswijk is dated posteriorly (17 May 2018) to the invitation for the oral proceedings before the Board (9 April 2018) and the proceedings before the Brussels Court was planned for the next day, on 27 November 2018. Said invitation to the proceedings before the Brussels Court was furthermore dated 6 November 2017; the representative had known therefore his unavailability at the date of 27 November 2018 already for a long time; in any case, the supporting attorney would have had the possibility to attend the oral proceedings before the Board on 26 November 2018, and to attend the next day the proceedings before the Brussels Court.

Hence, the request does not meet the requirements of postponement of oral proceedings as set out in the Notice of the Vice-President DG3, Supplementary publication 1, OJ EPO, 2018, VII.1.

2. Main request - Inventive step

2.1 The invention relates to compositions for the treatment of dermatological diseases where epidermal barrier formation and/or recovery has beneficial effects. The skin diseases and skin conditions are selected from inflammatory skin diseases, increased fibroblast proliferation, pruritus, physical damage of the skin surface, xerosis, bruises, hyperproliferation states of the skin, and transepidermal water loss. According to a more preferred embodiment, the inflammatory skin disease is psoriasis, atopic dermatitis, or various types of eczema.

2.2 D3 was cited as closest prior art in the decision of the examining division.

D3 discloses a composition comprising a zeolite, a stinging nettle leaf extract, and magnesium and/or calcium salts for the treatment of inflammatory skin diseases, such as psoriasis, neurodermitis, acne and dermatitis (see page 1 and the claims).

The zeolite can be heulandite/clinoptilolite, natrolite or thomsonite, and the calcium/magnesium is preferably a dolomite ($\text{CaMg}(\text{CO}_3)_2$). The composition can be used topically or orally (claims 19, 20). Example 2 relates to the treatment of psoriasis with a topical ointment comprising heulandite/clinoptilolite used in combination with an oral capsule of 25% nettle leaf extract and 75% heulandite/clinoptilolite. This example shows explicitly that the topical application of heulandite/clinoptilolite in the form of a powder, a cream or a bath solution has an effect on psoriasis, and leads to a 100% normalisation of the affected skin area, which means implicitly and inherently a skin recovery.

Claim 1 of the main requires the presence of a magnesium salt, wherein the amount of magnesium ions is in an amount higher than the calcium ions.

2.3 According to the appellant, the effect of the claimed composition surpasses that of the mere sum of the individual components, i.e. the composition exerts a synergistic effect on the establishment and/or the recovery of the epidermal barrier. The problem might be seen as the provision of a composition providing a synergistic effect on the establishment and/or the recovery of the epidermal barrier.

2.4 The solution is an association between clinoptilolite and a magnesium salt, wherein the molar amount of magnesium ions is higher than the molar amount of calcium ions.

2.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect.

Annex I and II have been filed to demonstrate said synergistic effect.

2.5.1 The experiments of Annex I show a comparison as to trans epidermal water loss (TEWL) between compositions comprising MgCl₂ (Series 1), CaCl₂ (Series 2), clinoptilolite-MgCl₂ (Series 3) and clinoptilolite-CaCl₂ (Series 4).

The composition according to the invention, namely the series 3 shows an average % of TEWL recovery comprised between 120% and 170%. The composition with MgCl₂ (Series 1) shows an effect comprised between 100% and 130%. The compositions comprising CaCl₂ and clinoptilolite-CaCl₂ show an effect inferior to 100%.

This document does therefore not present any comparison between a composition according to the invention, and two compositions comprising either MgCl₂ or clinoptilolite as such, and, for this reason, cannot support the existence of a synergistic effect linked with the association between magnesium ions and clinoptilolite. More particularly, the fact that there is no comparison made with a composition comprising uniquely clinoptillolite invalidates these tests as a comparison over the prior art D3.

The Board notes furthermore that the "series 4", namely the compositions as claimed provide an effect which is indeed superior to the effect provided by compositions comprising MgCl₂ ("Series 1"), or by compositions comprising CaCl₂-clinoptilolite ("Series 4") and compositions comprising CaCl₂ ("Series 2"). In view of the quantified maximal effects obtained by the "Series 3", "Series 1" and "Series 4", a synergistic effect is however not apparent or even credible.

2.5.2 Annex II was filed to demonstrate that a combination of zeolite and magnesium provides a synergistic effect when it comes to epidermal barrier recovery, which surpasses the effect of the two ingredients alone, and which could not be seen when zeolite, magnesium and calcium were combined with an excess of calcium.

These experiments show the effects of 10 formulations on epidermal barrier repair following SDS-induced barrier damages. The results are shown in the form of pictures, and are therefore not quantified. It is therefore impossible to state the existence of a synergistic effect linked with the use of a composition comprising clinoptilolite-MgCl₂.

- 2.5.3 In the absence of any demonstrated synergistic effect, the problem must be reformulated as the provision of compositions having an improved effect on the establishment and/or the recovery of the epidermal barrier.

Magnesium ions were known from the prior art to accelerate skin recovery, either alone or to a less extent when associated with Ca ions (see D7, the Abstract).

The association of magnesium to clinoptilolite, with an excess of magnesium ions appears to be obvious, in order to improve the effect reached with the use of clinoptilolite alone.

The claimed solution does not appear to be inventive over the teaching of D3 associated with D7, and the main request does not meet the requirements of Article 56 EPC.

3. Auxiliary request I

Claim 1 of auxiliary request I has been amended by the feature "and whereby said composition has a negative zeta potential and is able to form an electric double layer in an aqueous medium". There is no effect associated with these technical features which has been demonstrated. Moreover the formation of an electric double layer appears to be inherent to the association between clinoptilolite and magnesium ions in a composition. Hence, said amendments do not have any incidence on the reasoning and conclusions on inventive step outlined for the main request, which apply mutatis mutandis to claim 1 of auxiliary request I.

Auxiliary request I does not meet the requirements of Article 56 EPC.

4. Auxiliary request II

Claim 1 of auxiliary request II has been further specified by the nature of the magnesium salt and its amount in the composition and by the amounts of water, namely "between 0.2 and 30% w/w% of magnesium chloride hexahydrate" and "between 30 and 80 w/w% of water". As for auxiliary request I, there is no effect demonstrated as regards these features. Moreover, magnesium chloride hexahydrate is the hydrated form of magnesium chloride, which is disclosed in D7.

The claimed subject-matter is therefore not inventive over D3 associated with D7, and auxiliary request II does not meet the requirements of Article 56 EPC.

5. Auxiliary request III

Claim 1 has been amended by the feature "for use in the formation and/or recovery of the epidermal barrier function in patients affected by an inflammatory disease or condition". In view of the disclosure of D3 and D7, this amendment has no impact on the assessment of inventive step. Consequently, auxiliary request III does not meet the requirements of Article 56 EPC.

6. Auxiliary request IV

In comparison to claim 1 of auxiliary request III, claim 1 of auxiliary request IV has been further restricted by the nature of magnesium salt and its amount in the composition and by the amounts of water,

namely "between 0.2 and 30% w/w% of magnesium chloride hexahydrate" and "between 30 and 80 w/w% of water". As already mentioned for auxiliary request I, there is no effect demonstrated as regards these features and magnesium chloride hexahydrate is the hydrated form of magnesium chloride, which is disclosed in D7.

Hence, the claimed subject-matter is not inventive over D3 associated with D7, and auxiliary request IV does not meet the requirements of Article 56 EPC.

7. Auxiliary request V

In comparison to claim 1 of the main request, claim 1 of auxiliary request V has been amended by the following features:

- i) a restriction as to the nature of magnesium salt and its amount in the composition and by the amounts of water, namely "between 0.2 and 30% w/w% of magnesium chloride hexahydrate" and "between 30 and 80 w/w% of water"
- ii) a restriction by the feature "and whereby said composition has a negative zeta potential and is able to form an electric double layer in an aqueous medium".
- iii) a restriction by the feature "for use in the formation and/or recovery of the epidermal barrier function in patients affected by an inflammatory disease or condition".

As regards feature i), there is no effect demonstrated and magnesium chloride hexahydrate is the hydrated form of magnesium chloride, which is disclosed in D7.

There is no technical effect associated with feature ii) which has been demonstrated; the formation of an electric double layer is inherent to the association

between clinoptilolite and magnesium ions in a composition. Hence, said amendment ii) does not have any incidence on the reasoning and conclusions on inventive step.

In view of the disclosure of D3 and D7, the feature iii) has no impact on the assessment of inventive step.

Hence, the claimed subject-matter is not inventive over D3 associated with D7, and auxiliary request V does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



B. Atienza Vivancos

J. Riolo

Decision electronically authenticated