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Datasheet for the decision of 23 May 2018

Case Number: T 2471/16 - 3.3.01

Application Number: 11196067.0

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Language of the proceedings: EN

Title of invention:

Pharmaceutical composition for dermal use comprising calcipotriol and betamethasone for treating psoriasis

Patent Proprietor:

Leo Pharma A/S

Opponents:

Teva Pharmaceutical Industries Ltd.
PENTAFARMA S.A.
Generics [UK] Limited (trading as Mylan)
Sandoz B.V.

Relevant legal provisions:

EPC Art. 56, 114
RPBA Art. 12(4)

Keyword:

Inventive step - (no)
Late-filed evidence - submitted with the statement of grounds of appeal

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2471/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 May 2018

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Appellant: (Opponent 2)	PENTAFARMA S.A. Rua da Tapada Grande no. 2 Abrunheira 2710-089 Sintra (PT)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Appellant: (Opponent 3)	Generics [UK] Limited (trading as Mylan) Building 4 Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Appellant: (Opponent 4)	Sandoz B.V. Veluwezoom 22 1327 AH Almere (NL)

Representative:	Greiner, Elisabeth df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Respondent: (Patent Proprietor)	Leo Pharma A/S Industriparken 55 2750 Ballerup (DK)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 6 October 2016 rejecting the opposition filed against European patent No. 2455083 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 455 083 was granted with nine claims. Claim 1 reads as follows:

1. A non-aqueous topical pharmaceutical composition in the form of an ointment, a cream, a lotion, a liniment or other spreadable liquid or semi-liquid preparation for dermal use in the treatment of psoriasis, sebopsoriasis or seborrhoic dermatitis in humans and other mammals, said composition comprising a first pharmacologically active component A consisting of calcipotriol and a second pharmacologically active component B consisting of betamethasome [sic] *or an ester thereof and at least one pharmaceutically acceptable carrier, solvent, or diluent.*

II. Three oppositions were filed against the patent, on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed (Article 100(a), (b) and (c) EPC).

III. By letter of 2 December 2015, the opposition division summoned the parties to attend oral proceedings on 7 July 2016.

IV. By letter of 13 April 2016, an intervention pursuant to Article 105 EPC was filed. The intervener requested accelerated opposition proceedings and stated that, to expedite proceedings, it relied exclusively on existing facts and arguments which had already been raised by the opponents. It also requested that the oral proceedings not be postponed but take place on

7 July 2016 as scheduled. By letter of 4 May 2016, the intervener (subsequently opponent 4) submitted comments on the issue of inventive step.

V. The documents cited in the course of the opposition proceedings included the following:

D6: ABPI Compendium 1998-99, Datapharm Publications Ltd, London 1998, pages 618-619, Dovonex Ointment

D8: Brit J Dermatol 138, 254-258 (1998)

D11: Curr Med Res Opin 27(1), 225-238 (2011)

D17: J Am Acad Dermatol 37, S55-S58 (1997)

D21: Nouv Dermatol 13(10), 746-751 (1994)

D28: J Am Acad Dermatol 38(6), 1010-1011 (1998)

D29: Dermatologic Clinics 13(4), 835-839 (1995)

D37: Feldman et al., Poster Abstract: Use of Combination Topical Products (Calcipotriene/ Betamethasone Dipropionate) is Associated With Less Use of Biologic Therapy for Psoriasis (undated; content based on data of 2006-2011)

VI. The decision under appeal is the decision of the opposition division, announced on 7 July 2016 and posted on 6 October 2016, rejecting the oppositions.

In the decision under appeal, the opposition division held that the intervention was admissible (which had not been contested by any of the parties) and was to be treated as an opposition (Article 105(2) EPC).

The grounds of opposition raised in the proceedings did not prejudice maintenance of the patent as granted.

In particular, the claimed subject-matter involved an inventive step starting from the disclosure of either document D8 or document D21. Both documents disclosed an effective topical treatment of psoriasis using

calcipotriol and an ester of betamethasone (D8: valerate; D21: dipropionate), involving the alternating administration of those components at different times of the day. The claimed subject-matter differed from that prior disclosure in that calcipotriol and betamethasone (or an ester thereof) were combined in a single topical formulation which was non-aqueous. The data presented in the opposed patent, further supported by the evidence of document D11, rendered it credible that the administration of the two pharmacologically active agents in a single composition entailed a better efficacy of the treatment. The objective technical problem was thus the provision of an improved topical combination treatment of psoriasis. In the light of the available prior-art documents it was not obvious that the simultaneous administration of calcipotriol and betamethasone as a fixed composition would provide a superior therapeutic benefit.

VII. The opponents (appellants) each lodged an appeal against that decision, requesting the revocation of the patent.

VIII. The following document, first sumbitted by appellant-opponent 4 with its statement setting out the grounds of appeal, remains pertinent to the present decision:

D46: Drug Development and Industrial Pharmacy 30(10), front page and pages 1095-1102 (2004)

IX. Oral proceedings were held on 23 May 2018 in the absence of appellant-opponent 1 and appellant-opponent 2, in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

X. The arguments presented by the appellants may be summarised as follows:

Admission of document D46

Document D46 had not been held back intentionally by appellant-opponent 4, who had, after all, intervened in the opposition proceedings at a late stage and only a short time before the oral proceedings took place. For that reason, it had lacked time to co-ordinate and familiarise itself with the case. Filing new citations on appeal in order to challenge a first-instance decision had to be considered normal behaviour for a losing party and did not constitute a tactical abuse of procedure. In compliance with the requirement of Article 12(2) RPBA, document D46 had been filed at the earliest opportunity in the appeal proceedings. The document should be taken into consideration by the board due to its high *prima facie* relevance with regard to the possible impact of the vehicle components on the efficacy of the pharmaceutical composition.

Inventive step assessment starting from document D21

The subject-matter defined in claim 1 of the main request differed from the combination treatment disclosed in document D21 in that the components were to be administered in a single topical formulation which was non-aqueous.

Since the feature "non-aqueous" had not been shown to provide a specific technical effect (such as storage stability) over the entire scope claimed, it must be regarded as arbitrary.

The clinical data presented in the patent in suit related to the comparison of a combination treatment using the claimed two-compound formulation with either

calcipotriol monotherapy or betamethasone monotherapy. Thus the data in the patent in suit did not provide a direct comparison with the starting point in the prior art, which was not monotherapy but a combination treatment involving the alternating administration of the two pharmacologically active components.

The respondent's contention that the therapeutic effect provided by the claimed composition was surprisingly higher than the effect achievable by the "alternating" combination treatment according to document D21 was speculative and not based on experimental data.

Since the alleged improvement in efficacy had not been rendered initially plausible by the patent or the original application documents, it should not be permissible for the respondent to rely for credibility on the supplementary post-published evidence of documents D37 or D11. Furthermore, the methodology employed in document D11, which related to a meta-analysis of clinical studies (including the study reported in D21), had only been developed after the relevant date of the patent in suit, and therefore its use should not be permissible in the assessment of inventive step.

Even if those documents were nevertheless to be taken into account, they too did not provide proof of the alleged technical effect, for the following reasons:

- The data reported in document D37 were irrelevant, since they were not based on a clinical assessment of patients and did not relate to a comparison with the specific alternating combination treatment according to document D21.

- The data presented in document D11 could not be regarded as conclusive; in particular, D11 did not show

a causal link between the improved therapeutic benefit observed and one of the technical features distinguishing the claimed subject-matter from the disclosure of D21, because various other factors might have affected the results of the clinical studies.

Were the board nevertheless to acknowledge that the data presented in document D11 showed improved efficacy of the specific two-compound formulation targeted by the meta-analysis, it had in any case not been rendered credible that such improvement was achieved over the entire scope claimed. As corroborated by the experimental data reported in document D46 (table 2), the composition of the vehicle had a marked impact on efficacy, and document D11 only related to one specific two-compound formulation with a particularly favourable vehicle composition.

Starting from the technical teaching of document D21, the objective technical problem was thus the provision of an alternative formulation for the treatment of psoriasis, or at best, the provision of a formulation for the treatment of psoriasis giving rise to better patient compliance. Arguably, those compositions covered by claim 1 which did not present good storage stability (such as the comparison ointment mentioned in paragraph [0039] of the patent specification) might have to be prepared extemporaneously, which would have a negative effect on patient compliance.

It was well known that a treatment regimen requiring the alternating application of two different compositions, as known from the prior art, might result in unsatisfactory patient compliance. The obvious remedy consisted in combining the two active agents in a single formulation which required less frequent product application. Such a two-compound formulation

could, in principle, be aqueous or non-aqueous. Since it was common knowledge that calcipotriol lacked stability in aqueous formulations at certain pH values, it would have been obvious to a person skilled in the art to develop a non-aqueous vehicle, which could be accomplished by routine work. Formulations of vitamin D analogs structurally similar to calcipotriol in non-aqueous vehicles were known. There was no evidence of a prejudice or a teaching in the prior art to the effect that the two pharmacologically active agents could not be combined in a single non-aqueous formulation. That the prior art only disclosed the alternating application of two separate products was due to the fact that the studies concerned had been conducted by clinicians relying on commercially available monotherapy products. For these reasons, the subject-matter of claim 1 was obvious having regard to the prior art.

XI. The arguments presented by the respondent may be summarised as follows:

Admission of document D46

When presenting document D46 in the appeal proceedings, appellant-opponent 4 had failed to give any reason why that document could not have been presented in the first-instance proceedings. Indeed, it appeared from a record on the document itself (see D46: bottom of front page) that it had been downloaded on 3 February 2016 and had thus been available to appellant-opponent 4 well before it intervened in the opposition proceedings in April 2016. It was not apparent that the document had suddenly acquired a higher relevance than before, due to any specific development in the case.

Inventive step starting from document D21

Unlike document D21, claim 1 of the patent in suit provided calcipotriol and betamethasone in a single non-aqueous formulation. The technical effect of that difference was an improvement in the combination therapy.

The data reported in the patent in suit, in particular in figure 4, with regard to therapeutic efficacy demonstrated a supra-additive effect of the claimed composition which was clearly more pronounced than the mere additive effect which would have been expected, based on the teaching of documents D21 or D8, from a combination treatment.

The hypothetical additive effect could be calculated on the basis of the data provided in the patent for each monotherapy regimen. Thus a comparison with the closest prior art was possible on the basis of the data provided in the patent in suit.

The appellants had not provided any experimental data to refute the results shown in the patent.

The two technical features distinguishing the claimed subject-matter from the disclosure of D21 were interlinked because the two active components could not be stably combined into a single composition in the presence of water, calcipotriol and betamethasone having contrary pH requirements for optimum stability. Thus the compositions covered by claim 1, including the "comparison ointment" according to example 2 (paragraphs [0039] and [0040]) of the patent in suit, were considerably more stable than an admixture of the monotherapy ointments mentioned in document D21 would be, because the non-aqueous nature of the compositions

removed the primary cause of instability, which would otherwise cause rapid deterioration.

The combined effect of the two distinguishing features of the claimed composition, namely improved psoriasis therapy over an alternating regimen known from the prior art, was explicitly mentioned in paragraph [0012] of the patent specification, and had since been confirmed by further data including data from clinical trials. In that context, documents D11 and D37 were relevant.

Document D11 presented a meta-analysis comparing seventeen different psoriasis treatments across nineteen clinical studies, the central link being a fixed comparison regimen involving the twice-daily application of calcipotriol. Among the seventeen treatments included in document D11 was the alternating combination treatment of the closest prior art D21 (mentioned as reference 43 in D11). The single combination preparation according to claim 1 of the patent in suit was mentioned in document D11 by the name "two-compound formulation" (or "TCF").

While, by its nature, a meta-analysis did not provide a direct comparison, mixed treatment comparison was a scientifically legitimate method when a randomised clinical trial was not available for direct comparison.

The results presented in D11 confirmed that the two TCF treatments (given once daily or twice daily) gave the best results measured by the PASI score. This could be derived from, in particular, figures 4 and 6 and the conclusions presented on pages 233 to 236 of D11.

The appellants' argument that document D11 did not show a causal link between the observed improved therapeutic benefit and one of the technical features

distinguishing the claimed subject-matter from the disclosure of D21, because various other factors might have affected the results of the clinical studies, was speculative and did not have an empirical basis.

Document D11 only considered studies which were well matched with regard to patient characteristics (D11: page 235). In the study according to document D21, it had been verified that patient compliance was good, without deviation from the study protocol (D21: page 749, point 3). The appellants' criticisms in this regard were therefore misplaced. Furthermore, it could be derived from document D46 that the vehicle composition could not have played a role: Document D46 compared the *in vitro* skin permeation of calcipotriol and betamethasone diproprionate from the Daivonex® and Diprosone® ointments used according to D21 with the permeation achieved with Daivobet® (also called Dovobet®) ointment, the commercialised two-compound formulation which had also been used in the TCF studies assessed in D11 (see D46: page 1097; column 1, "Test Formulations"). According to table 2 on page 1099 of D46, the permeation results were the same for the commercially available TCF (ointment 5) and for the monotherapy ointments. Thus document D46 supported the respondent's position by showing that the improvement found according to document D11 for the single formulation treatment (TCF) versus D21 could not have been due to the vehicle composition.

Further support for an improvement relative to separate calcipotriol/steroid regimens (such as D21) came from document D37. Patients for whom topical combination therapy was inadequate typically moved on to treatment with a biologic agent, e.g. an antibody therapy. The authors of document D37 studied how often a patient's topical treatment for psoriasis was supplemented with a

systemic biologic agent within a year. In more than 6000 patients, only 4.7 % required the supplement when using a two-compound formulation in conformity with claim 1, whereas that figure was about 10% in patients who applied calcipotriol and a steroid separately. Moreover, supplementation could be deferred longer when using the claimed invention. While D37 did not explicitly refer to betamethasone, it referred to class 1 and 2 steroids (which included betamethasone) and generally confirmed the data provided in the patent.

The objective technical problem should therefore be defined as the provision of an improved treatment in the therapy of psoriasis.

Starting from the technical teaching of document D21, many possibilities might be envisaged for solving the technical problem, such as variations in the treatment regimen and dosages, but providing a combined composition was not an obvious way of solving the technical problem.

It was only with hindsight that the skilled person would consider applying the active components at the same time. In the prior art (*inter alia*, D8 or D21) there was nothing to suggest that there could be a benefit in applying the pharmacologically active components simultaneously. Furthermore, the prior art (specifically documents D17, D28 and D29) warned against combining calcipotriol and other agents in the same composition.

Avoiding water hugely increased the shelf life, but none of the prior-art documents suggested using a non-aqueous vehicle. All prior-art calcipotriol ointments included water. D29 stated that calcipotriol required a

relatively high pH to be stable. The person skilled in the art would infer from this that water was essential for formulating calcipotriol, which was not known to be functional in non-aqueous formulations.

XII. The appellants requested that the decision under appeal be set aside and the patent be revoked.

XIII. The respondent requested that the appeals be dismissed.

Reasons for the Decision

1. Admissibility of the appeals

The appeals comply with Articles 106 to 108 EPC and Rule 99 EPC and are therefore admissible.

2. Admission of document D46 (Article 114 EPC and Article 12 RPBA)

2.1 Document D46 was filed by appellant-opponent 4 with its statement setting out the grounds of appeal (see point VIII above). Pursuant to Article 12(1), 12(2) and 12(4), second half-sentence, RPBA, it is thus, in principle, to be taken into account in the proceedings.

2.2 Article 12(4), first half-sentence, RPBA, however, confers on the board the discretionary power to hold inadmissible evidence which could have been presented in the first-instance proceedings. This provision, in line with Article 114(2) EPC, is basically intended to forestall tactical abuse.

2.3 It appears from the documents on file that appellant-opponent 4 intervened in the opposition proceedings only at a late stage and relied on the submissions and evidence already presented by the other opponents, so

as not to cause any delays such as postponement of the scheduled oral proceedings (see point IV above).

The argument that the available evidence did not support an improvement in therapeutic efficacy of the claimed composition over the entire scope claimed was put forward during the discussion of inventive step (see the minutes of the oral proceedings of 7 July 2016, point 8.12) but was eventually rejected by the opposition division.

2.4 In view of the foregoing, the board considers that appellant-opponent 4 had plausible reasons not to file further pieces of evidence at the time when it intervened in the first-instance proceedings.

Also, presenting with the statement setting out the grounds of appeal a new document to reinforce the line of attack already taken before the department of first instance is normal behaviour for a losing party.

Hence the board sees no evidence of negligence or abusive tactical behaviour of the appellant and thus sees no compelling argument for holding document D46 inadmissible pursuant to Article 12(4) RPBA.

2.5 It is furthermore within the board's discretion pursuant to Article 114(1) and (2) EPC to consider a document which has been brought to its attention in view of its relevance.

In this instance, the board considers document D46 to be of high *prima facie* relevance, since it reports experimental data relating to skin permeation results of calcipotriol and betamethasone dipropionate obtained with different vehicle compositions. That information is pertinent to the question whether any vehicle composition in conformity with claim 1 would provide

the same high efficacy of treatment as the two-compound formulation according to document D11, which was a central issue in the assessment of inventive step (see point 3.8.4 below).

2.6 For these reasons, the board did not hold document D46 inadmissible (Article 12(4) RPBA), but decided to take it into account in the appeal proceedings (Article 114 EPC and Article 12(1) and (2) RPBA).

3. Inventive step (Articles 100(a), 52(1) and 56 EPC)

Patent in suit

3.1 The patent in suit (see paragraphs [0001] to [0007] of the patent specification) aims to provide pharmaceutical compositions for dermal use in the treatment of psoriasis and related skin diseases which combine two pharmacologically active components, namely a vitamin D analogue and a corticosteroid, in a single formulation, in order to facilitate patient compliance. The patent acknowledges that in the prior art psoriasis was treated with a combination of calcipotriol (a vitamin D analogue) and betamethasone dipropionate or valerate (a corticosteroid component). The two drugs had not been previously combined in a single formulation, due to potential stability issues, as each drug has optimum stability at a different pH. Rather, the drugs were administered alternately in separate preparations at different times of the day.

3.2 Claim 1 as granted (see point I above) defines a single non-aqueous composition for dermal use in the treatment of psoriasis, sebopsoriasis or seborrhoic dermatitis containing a combination of the vitamin D analogue calcipotriol ("pharmacologically active component A") and, as the corticosteroid component, betamethasone

or an ester thereof ("pharmacologically active component B").

Starting point in the prior art

3.3 It is common ground that document D21 is a suitable starting point for the assessment of inventive step.

3.4 Document D21 relates to a clinical trial in which 188 psoriasis patients were treated for six weeks either by one application of calcipotriol ointment (Daivonex®) in the morning and one application of betamethasone dipropionate ointment (Diprosone®) in the evening (combination treatment) or by twice-daily application of calcipotriol ointment (calcipotriol monotherapy). D21 reports that, using the Psoriasis Area Severity Index (PASI) as the main criterion to evaluate the efficacy of the treatment, a faster and more substantial improvement was seen with the alternating combination treatment, which was also better tolerated. D21 concludes that the two drugs, which have different molecular mechanisms of action, complement each other with regard to efficacy and tolerance (see D21: Summary and page 746, left column: Introduction).

3.5 It was uncontested that the Daivonex® ointment, also known as Dovonex®, contained water (see document D6).

Objective technical problem and solution

3.6 The subject-matter of claim 1 as granted differs from the disclosure of document D21 firstly in that component A (calcipotriol) and component B (betamethasone or an ester thereof) are present in a single composition, and secondly in that said single composition is required to be non-aqueous.

3.7 Non-aqueous nature of the composition

The respondent maintained that avoiding water removed the primary cause of rapid instability of the pharmacologically active components.

Considering that calcipotriol and betamethasone require different pH values for maximum stability (as also mentioned in paragraph [0005] of the patent specification), choosing a non-aqueous vehicle would indeed appear to be a plausible measure for preventing pH-related stability issues. However, the patent in suit does not contain experimental data on drug stability obtained from a direct comparison of aqueous and non-aqueous formulations.

The board furthermore considers that the available data do not permit the conclusion to be drawn that any non-aqueous vehicle covered by the definition of the composition in claim 1 would achieve satisfactory long-term storage stability of the pharmacologically active components: For instance, as reported in example 2 of the patent in suit (paragraphs [0039] and [0040]), in a non-aqueous ointment containing calcipotriol and betamethasone dipropionate in a vehicle composed of white soft paraffin, lanolin and propylene glycol, the calcipotriol did not remain stable during storage but was degraded almost completely under the test conditions. Thus it would appear that, besides water, certain non-aqueous vehicle components too may have an impact on stability.

Compositions which do not achieve a particularly long shelf life are not excluded from the scope claimed by any explicit condition. Nor are they excluded implicitly, since they may nevertheless be of use, in particular when freshly prepared, in the treatment of psoriasis.

Hence, while the choice of a non-aqueous vehicle may contribute to the stability of the pharmacologically active agents in the formulation, the patent in suit does not provide evidence that a particular technical effect is obtained on that account over the entire scope claimed.

3.8 Two-compound formulation

With regard to the claimed combination of both pharmacologically active components A (calcipotriol) and B (betamethasone or an ester thereof) in a single formulation, the respondent contended that an unexpected improvement in therapeutic efficacy, namely a "supra-additive" effect greater than the expected mere additive effect of the individual components, was obtained when such compositions were administered to patients.

The board does not reach the same conclusion, for the following reasons:

3.8.1 Assessment of the data provided in the patent in suit

While it is mentioned in paragraph [0012] of the patent specification that the preparation of the invention provides "a success of treatment of psoriasis hitherto unattainable", in particular "by alternating treatment" with "commercial preparations containing either calcipotriol or betamethasone", that statement is not however backed up by experimental data showing a direct comparison with alternating combination treatment.

Instead, the clinical trial data provided in the patent relate to the comparison of the administration of a single non-aqueous composition according to claim 1 containing both component A (calcipotriol hydrate) and component B (betamethasone dipropionate) with monotherapy regimens involving either the exclusive

administration of a composition containing only component A (calcipotriol hydrate) or the exclusive administration of a composition containing only component B (betamethasone dipropionate).

The respondent argued that the required comparison between the administration of the two-compound formulation according to the patent in suit with alternating combination treatment according to D21 could nevertheless be derived from the data presented in the patent:

- In that context, the respondent referred to document D8, which discloses a treatment regimen alternating the application of calcipotriol (once daily in the morning) and betamethasone valerate (once daily in the evening). Document D8 (see page 257: "Discussion") contains the following statement: "As calcipotriol and betamethasone valerate work by interacting with differenct receptor subtypes (vitamin D or glucocorticoid receptors), an additive or synergistic effect could theoretically be expected." D8 goes on to confirm that there is such an additive effect, since the results obtained in a clinical trial with the combination therapy were better than those obtained with calcipotriol monotherapy.

- The respondent argued that the person skilled in the art would infer from this and from the similar teaching in document D21 that an additive effect could be expected when both components were administered (be it in the same formulation or by alternating treatment). Turning to the data reported in the patent in suit (in particular in figure 4), that hypothetical additive effect could be calculated from the results obtained by monotherapy with each component. It could then be compared with the effect which had actually been observed when the two-compound formulation according

to the invention was administered. The actual effect reported in figure 4 of the patent in respect of overall response and onset of healing turned out to be more favourable than the calculated "expected" effect. Thus it could be inferred from the data presented in the patent that the actual effect obtained with the combination product surprisingly surpassed the expected additive effect, to yield a supra-additive effect.

Irrespective of the fact that D8 relates to betamethasone valerate rather than to the dipropionate, the board does not find this line of argument convincing, since the teaching of D8 neither suggests nor shows an additive effect which corresponds in its magnitude exactly to a theoretical combined effect of the monotherapies. Document D21, meanwhile, does not mention an "additive" effect at all but merely reports that, in comparison with calcipotriol monotherapy, a faster and more substantial improvement of the PASI score was seen with the combination treatment. The board observes in that context that the clinical studies described in documents D8 and D21 did not involve a comparison with betamethasone monotherapy, but only with calcipotriol monotherapy. The person skilled in the art reading D8 and D21 would have no specific reason to assume that a general reference in document D8 to an expected "additive" effect, or in document D21 to the "complementary" activity of the two drugs and a possible potentiation of their efficacy (see page 746: "Introduction") could be meant as an exact quantitative prediction, as suggested by the respondent. Thus the respondent's case is based on nothing more tangible than a very narrow interpretation of the word "additive".

On the basis of the available data it cannot be ruled out that the alternating morning/evening combination treatment and the combination treatment using a single two-compound formulation have the same therapeutic efficacy. In the absence of experimental data in the patent showing a direct comparison of those regimens, the respondent's allegation that the combination product provides superior therapeutic efficacy cannot be verified.

3.8.2 Supplementary evidence

This gives rise to the question whether it is permissible for the respondent nevertheless to rely on supplementary post-published data, as provided in documents D11 and D37.

The patent in suit is concerned with the efficacy of a combination treatment in which the combination of calcipotriol and betamethasone is to be administered in a single formulation to treat psoriasis and related skin diseases, and, in figures 1 to 4, provides experimental data on treatment efficacy, compared with the monotherapies using each component alone.

When comparing the claimed combination product with the closest prior art, its alleged technical effect (namely, improved efficacy in comparison with "alternating" combination treatment) still concerns the successful treatment of psoriasis and is, moreover, mentioned in a general way in the patent in suit (in particular, in paragraph [0012]; see point 3.8.1 above). Hence it appears reasonable that the respondent should be permitted to provide further data in support of that subsequently invoked but closely related technical effect.

3.8.3 Assessment of the data provided in document D37

The comparison presented in document D37 is not based on data from a clinical study, but on a retrospective analysis of "national claims data from 2002 to 2011". Psoriasis patients who were prescribed a topical combination product containing calcipotriol and betamethasone dipropionate are compared to patients who received both topical medication containing calcipotriene and topical medication containing class 1-2 steroids. D37 does not give further details concerning the treatment regimen or the specific steroids applied in the comparative group.

Since the patients in the comparative group did not necessarily receive betamethasone, and it cannot be verified whether an alternating treatment regimen such as that in document D21 was observed, the board considers that the comparative group of D37 is not adequately representative of the closest prior art D21. That alone is reason enough to find that document D37 cannot provide conclusive data in support of the alleged technical effect.

3.8.4 Assessment of the data provided in document D11

Contrary to the appellants' view, the board is of the opinion that document D11 cannot be excluded from consideration on the ground that the methodology used for the meta-analysis of D11 may have been developed only after the relevant date of the patent in suit. What matters is that D11 is concerned with the assessment of data which may be pertinent as evidence of the alleged technical effect. Thus, in view of the considerations in point 3.8.2 above, the data in D11 may be used in the assessment of inventive step.

In the meta-analysis according to document D11, the efficacy of a specific two-compound formulation (see D11: page 226, left column, lines 8 to 14) was assessed in comparison with other topical treatments:

"The two-compound formulation (TCF) product is a topical ointment containing calcipotriol (50 µg/g) and betamethasone dipropionate (BDP) (0.5 mg/g) and is licensed to be applied once daily."

According to the respondent, the specific "licensed" two-compound formulation of D11 was Dovobet® (also called Daivobet®) ointment, which conformed to the definition of claim 1 of the patent in suit and corresponded in its non-aqueous vehicle composition to "ointment 5" described in document D46 (see page 1097: Test Formulations").

The board assumes in the respondent's favour that the meta-analysis was conducted correctly and that the data presented in figure 6 of document D11 show an improvement in therapeutic efficacy achieved with the specific two-compound formulation ("TCF once daily"), as opposed to the alternating combination treatment according to the closest prior art D21 ("Calcipotriol od + betamethasone dipropionate od").

However, the appellants' counterargument that it has nevertheless not been rendered credible that an improvement in therapeutic efficacy will be obtained with all compositions covered by the scope of claim 1 is substantiated by the data shown in document D46:

The aim of the formulation study described in document D46 was to combine the two drug components in a single formulation and, in addition, achieve a skin delivery similar to the marketed monotherapy products, Daivonex® ointment and Diproderm® ointment

(i.e. the monotherapy ointments which were used according to the closest prior art D21 in an alternating regimen; see point 3.4 above). According to D46, the effect of different non-aqueous vehicle compositions was to be investigated. In table 2 on page 1099, document D46 presents *in vitro* skin permeation data for calcipotriol and betamethasone dipropionate, as achieved with various different ointment compositions. Daivonex® ointment is included as the reference product for calcipotriol, and Diproderm® ointment as the reference product for betamethasone dipropionate.

Ointment 5, which was based on a vehicle of paraffin containing 5% polyoxypropylene-15 stearyl ether (PSE), achieved the same flux rates and lag times as obtained for each component with the corresponding monotherapy reference product. However, other non-aqueous vehicles did not achieve the same results: In particular, ointments 1 and 2, which contained calcipotriol and betamethasone propionate in paraffin vehicles containing 5% and 10% of isopropyl myristate (IPM), as opposed to 5% PSE, were found to decrease the permeation rate to about 25% to 35% compared with the reference products. Document D46 concludes that the choice and amount of solvent had a significant influence on skin permeability, and that especially the solvent PSE had a marked influence.

This means that the two-compound formulation assessed in the meta-analysis of document D11 had especially favourable skin delivery properties due to its vehicle composition, which contained PSE (see above: point XI, page 10, first full paragraph and point 3.8.4, third paragraph). Skin delivery may certainly be regarded as a factor which has an impact on therapeutic efficacy;

after all, that is why skin permeation data were determined in D46. For that reason, the board agrees with the appellants' argument that it has not been rendered credible by the meta-analysis of document D11 that any non-aqueous composition covered by the scope of claim 1, especially those containing solvent components less suitable than PSE, would provide improved therapeutic benefit over the alternating combination regimen disclosed in document D21.

3.8.5 As a further technical effect, the patent in suit mentions that it was an object of the invention to alleviate the inconveniences of a two-component or multi-component regimen, known to have have a negative impact on patient compliance (see paragraphs [0006] and [0007] of the patent specification).

3.9 In view of these considerations, the objective technical problem to be solved when starting from the teaching of document D21 can be defined as the provision of a further topical treatment for psoriasis, sebopsoriasis or seborrhoic dermatitis involving the combination of calcipotriol and betamethasone as the pharmacologically active components, suitable for facilitating patient compliance.

3.10 It was common ground that the combination of calcipotriol and betamethasone is useful in the treatment of psoriasis.

In view of the indications for which both drugs have commonly been known, the board finds it credible that a therapeutic benefit may also be expected in the treatment of sebopsoriasis and seborrhoic dermatitis, but this was anyway irrelevant for the outcome of the present decision.

Obviousness of the solution

3.11 According to the patent in suit (see paragraphs [0002] to [0007]), topical combination treatment with calcipotriol and betamethasone was known. Since it was also well known that these two drug components achieved their maximum stability at different pH values, they were formulated and applied in separate preparations, e.g. in an alternating sequence (as also described in document D21). Due to the inconvenience of observing a two-component regimen, patient compliance was, "needless to say", a problem.

3.12 Based on that common background knowledge, the person skilled in the art would have had an incentive to develop a single combination product comprising both pharmacologically active components in one composition with a view to providing a further treatment option and facilitating patient compliance.

This evident want of such a single formulation, and the approach of trying for one, is corroborated by the teaching of document D28. D28 starts by mentioning that calcipotriol is a widely prescribed topical treatment for psoriasis. For better convenience, pharmacists and patients have been known to mix calcipotriol ointment and other psoriasis medications in a single container. Calcipotriol, however, is inactivated by an acidic pH and can be unstable when mixed with other topical preparations (see D28: page 1010, column 1, paragraph 1).

Hence, contrary to the respondent's view, it is not only with hindsight that the person skilled in the art would consider applying the two pharmacologically active components simultaneously. Document D28 illustrates that this is in fact an obvious idea for

improving convenience which had previously occurred to pharmacists and patients, but cautions against the extemporaneous mixing of pre-formulated monotherapy products. A pharmaceutical formulator, however, is in a different position from that of a patient and can take account of potential incompatibilities by formulating a suitable combination product from scratch, instead of simply desisting from mixing pre-formulated marketed monotherapy products.

3.13 The person skilled in the art would not have been discouraged from formulating a single combination product by the incompatible stability pH profiles of the pharmacologically active components. Rather, it would have been an obvious measure to try and formulate a suitable non-aqueous vehicle in order to minimise potential pH-related stability issues. The board is of the opinion that such formulation work does not go beyond the usual routine work of a pharmaceutical formulator.

3.14 The incentives in favour of a single non-aqueous formulation would have been at work irrespective of the board's finding that not all non-aqueous vehicles ultimately turned out to provide long-term storage stability (see example 2 of the patent and point 3.7 above).

3.15 The board does not find the respondent's counterarguments convincing, for the following reasons:

3.15.1 The prior art does not teach that calcipotriol and betamethasone (or esters thereof) cannot be combined in the same formulation. Rather, the documents cited in that context by the respondent acknowledge that calcipotriol may be destabilised by an acid pH, and generally advise that it should not be mixed with

incompatible drugs or vehicles (see D17: final sentence; D28: opening paragraph; D29: page 838, right column). Since the relevant text passages do not state or suggest at any point that calcipotriol is incompatible with betamethasone, the respondent's argument must fail.

3.15.2 According to the respondent, all prior-art calcipotriol formulations included water, which would strongly imply to the skilled person that it was an essential component for formulating that molecule. In particular, the marketed Dovonex® ointment and Dovonex® cream (as disclosed in document D6) contained water. Document D29 stated on page 838 that calcipotriol "required" a relatively high pH.

The board considers that the mere fact that certain known calcipotriol formulations contained water does not amount to a technical teaching that water is essential in such formulations, or that calcipotriol would not function in a non-aqueous vehicle. Moreover, the statement in document D29 obviously relates to aqueous formulations and cannot be taken to infer that non-aqueous formulations are for any reason undesirable.

3.16 For these reasons, the board has concluded that it would have been obvious for the person skilled in the art to formulate a two-compound formulation containing both calcipotriol and betamethasone or an ester thereof, and to choose a non-aqueous vehicle, in order to solve the objective technical problem (see point 3.9 above).

3.17 As a consequence, the subject-matter of claim 1 as granted does not involve an inventive step within the meaning of Article 56 EPC.

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:

L. Malécot-Grob A. Lindner

Decision electronically authenticated