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Datasheet for the decision of 3 December 2020

Case Number: T 2708/19 - 3.3.07

Application Number: 08844931.9

Publication Number: 2214642

IPC: A61K9/00, A61K31/196, A61K9/06, A61K9/107

Language of the proceedings: EN

Title of invention:
TOPICAL COMPOSITION

Patent Proprietor:
GSK Consumer Healthcare S.A.

Opponents:
Prüfer & Partner mbB
Kern Pharma, S.L.

Headword:
TOPICAL COMPOSITION/GSK Consumer Healthcare S.A.

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 56

Keyword:
Admission of new documents (Yes)
Admission of auxiliary requests 1-4 (Yes)
Inventive step - All requests (No)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2708/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 December 2020

Appellant: (Opponent 1)	Prüfer & Partner mbB Sohnckestrasse 12 81479 München (DE)
Representative:	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Appellant: (Opponent 2)	Kern Pharma, S.L. Pol. Ind. Colom II C/ Venus, 72 08228 Terrassa (ES)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Respondent: (Patent Proprietor)	GSK Consumer Healthcare S.A. Route de l'Etraz 2 1197 Prangins (CH)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 1 August 2019 concerning maintenance of the European Patent No. 2214642 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 2 214 642 was granted on the basis of a set of 8 claims.

II. The patent was opposed under Article 100(a), (b) and (c) EPC, on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division that the patent in amended form meets the requirements of the EPC. The decision was based on the main request filed with letter of 19 June 2018.

Independent claim 1 of the main request read:

"1. A topical pharmaceutical composition, which is in the form of an opaque emulsion-gel, and which comprises
(a) 2-4% (w/w) of diclofenac diethylammonium salt,
(b) 0.5-2% (w/w) of a saturated or unsaturated C10-C18 fatty alcohol selected from the group consisting of stearyl alcohol, myristyl alcohol, lauryl alcohol and oleyl alcohol;
(c) at least 40% (w/w) of water,
(d) 10-30% (w/w) of at least one C2-C4 alkanol,
(e) 3-15% (w/w) of at least one glycol solvent selected from the group consisting of 1,2-propanediol and polyethylene glycol (200-20000),
(f) 0.5-5% (w/w) of at least one gelling agent selected from the group consisting of carbomers,
(g) 2-8% of at least one liquid lipid forming the oily phase of the emulsion-gel,

(h) 1-3% of at least one non-ionic surfactant, and
(i) a basic agent to adjust the pH of the total composition to 6-9."

IV. The documents cited during the opposition proceedings included the following:

D1: US 4,917,886
D2: WO 2004/030665 A1
D4: "Percutaneous Penetration Enhancers" Taylor and Francis, 2006, Ed .2, Chapter 12, 137-138, 153-154
D8: Rote Liste 2007, "Voltaren® Emulgel®". 05 540
D16: EP 1 457 202 A2

V. According to the decision under appeal, the main request met the requirements of Article 123(2) EPC and the requirements of sufficiency of disclosure.

As regards inventive step, D1 was considered as the closest prior art, especially in view of example 2. D8 and D16 were less suitable as closest prior art, since having less features in common with the claimed composition. D8 related to the commercial product Voltaren® Emulgel®.

Claim 1 of the main request differed from example 2 of D1 in that the composition comprised a saturated or unsaturated C10-C18 fatty alcohol and a higher amount of diclofenac diethyl ammonium salt (DDEA).

The data in Tables 1-4 of the patent allowed a direct comparison with the closest prior art and showed an improved technical effect as to the skin permeation.

The problem was defined as the provision of a topical stable composition comprising higher amounts of DDEA

and having improved skin permeation. The solution was not obvious and the subject-matter of claims 1-7 of the main request met the requirements of Article 56 EPC.

VI. Opponent 01 and opponent 02 (hereinafter appellants 01 and 02) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal appellant 02 submitted *inter alia* the following items of evidence:

A27: Declaration of Prof. Isidoro Caraballo
A32: Voltarene Emulgel 1% gel, French monograph, December 14th, 2008
A33: Diclofenaco Kern Pharma 1% Emulgel, letter of the Spanish Medicines Agency, February 2nd, 2009

VIII. With a letter dated 16 April 2020, the patent proprietor (hereinafter the respondent) submitted auxiliary requests 1-4 and the following items of evidence:

A4': Full Chapter 12 of D4
A34: Declaration of Rickard Sigerud
A35: Declaration of Graeme Clark
A36: Study report "Comparison of Voltaren Emulgel 1.16% versus Voltaren Emulgel 2.32%

The subject-matter of the independent claim 1 of the auxiliary requests read as following, difference(s) compared with claim 1 of the main request shown in bold:

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Auxiliary request 1

"1. A topical pharmaceutical composition, which is in the form of an opaque emulsion-gel, and which comprises
(a) **2-2.5%** (w/w) of diclofenac diethylammonium salt,
(b) **0.7-1%** (w/w) of a saturated or unsaturated C10-C18 fatty alcohol selected from the group consisting of stearyl alcohol, myristyl alcohol, lauryl alcohol and oleyl alcohol;
(c) **60-70%** (w/w) of water,
(d) **15-20%** (w/w) of at least one C2-C4-alkanol,
(e) **3.5-6%** (w/w) of at least one glycol solvent selected from the group consisting of 1,2-propanediol and polyethylene glycol (200-20000),
(f) **0.9-1.8%** (w/w) of at least one gelling agent selected from the group consisting of carbomers,
(g) **4-6%** (w/w) of at least one liquid lipid forming the oily phase of the emulsion-gel,
(h) **1.5-2.5%** (w/w) of at least one non-ionic surfactant, and
(i) 0.5-2% (w/w) of a basic agent to adjust the pH of the total composition to **6.5-8**, **wherein the basic agent is diethylamine**."

Auxiliary request 2

"1. A topical pharmaceutical composition, which is in the form of an opaque emulsion-gel, and which comprises
(a) **2-2.5%** (w/w) of diclofenac diethylammonium salt,
(b) **0.7-1% (w/w) of oleyl alcohol;**
(c) **60-70%** (w/w) of water,
(d) **15-20%** (w/w) of ethanol, isopropanol or mixtures thereof,

(e) **3.5-6%** (w/w) of at least one glycol solvent selected from the group consisting of 1,2-propanediol and polyethylene glycol (200-20000),
(f) **0.9-1.8%** (w/w) of at least one gelling agent selected from the group consisting of carbomers,
(g) **4-6%** (w/w) of at least one liquid lipid forming the oily phase of the emulsion-gel,
(h) **1.5-2.5%** (w/w) of at least one non-ionic surfactant, and
(i) **0.5-2% (w/w) of diethylamine to adjust the pH of the total composition to 6.5-8."**

Auxiliary request 3

"1. A topical pharmaceutical composition, which is in the form of an opaque emulsiongel, and which comprises
(a) **2-2.5**% (w/w) of diclofenac diethylammonium salt,
(b) **0.7-1% (w/w) of oleyl alcohol;**
(c) **60-70%** (w/w) of water,
(d) **15-20% (w/w) of isopropanol,**
(e) **3.5-6% (w/w) of 1,2-propanediol,**
(f) **0.9-1.8%** (w/w) of at least one gelling agent selected from the group consisting of carbomers,
(g) **a liquid lipid forming the oily phase of the emulsion-gel, consisting of 22.8% (w/w) of liquid paraffin and 2-2.8% (w/w) of coco-caprylate/caprate,**
(h) **1.5-2.5% (w/w) of at least one non-ionic surfactant, which is a polyoxyethylene (10-30) fatty alcohol ether**, and
(i) **0.5-2% (w/w) of diethylamine to adjust the pH of the total composition to 6.5-8."**

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Auxiliary request 4

"1. A topical pharmaceutical composition, which is in the form of an opaque emulsion-gel, and which consists of
(a) **2.32%** (w/w) of diclofenac diethylammonium salt,
(b) **0.75% (w/w) of oleyl alcohol;**
(c) **64.26%** (w/w) of purified water,
(d) **17.50% (w/w) of isopropanol,**
(e) **5.00% (w/w) of 1,2-propanediol,**
(f) **1.70% (w/w) of Carbomer 980,**
(g) **2.50% (w/w) of liquid paraffin and 2.50% (w/w) of coco-caprylate/caprate,**
(h) **2.00% (w/w) of polyoxyethylene-20-cetostearyl ether,**
(i) **1.35% (w/w) of diethylamine,**
(j) **0.02% (w/w) of butylhydroxytoluene,** and
(k) **0.10% (w/w) of perfumes."**

IX. In a communication pursuant to Article 15(1) RPBA, the Board, in line with the approach followed by the respondent, stated that it was inclined to take the composition of Voltaren® Emulgel®, as shown by D8 and its complementary information given by A32, A33 and A35, as the closest prior art for the assessment of inventive step, in view of the number of technical features in common with the claimed invention.

X. Oral proceedings took place on 3 December 2020.

XI. The arguments of the appellants may be summarised as follows:

Admission of documents A34 and A36 into the proceedings

According to appellant 01, A34 was a late filed document without relevant information. It had been filed as an alleged proof for the public access to the qualitative and quantitative composition of Voltaren® Emulgel® before the priority date of the opposed patent. This was information that had been available to the patentee in the time of the first instance proceedings. A34 pertained to information from the Swedish regulatory register that was allegedly publicly accessible from 1 July 2005 to November 2007. This information allegedly contained not only the qualitative, but also the quantitative composition of Voltaren® Emulgel®. But there was no proof for this allegation.

A36 could have been filed several years earlier and in fact was withheld by the patentee, who therefore avoided a discussion of A36 already in first instance. A36 was *prima facie* not relevant since it did not provide an exact comparison between the product Voltaren® Emulgel® and the claimed compositions.

Main request - Inventive step

According to appellant 01, D1 was the closest prior art rather than Voltaren® Emulgel®. The exact composition of Voltaren® Emulgel® was not clearly identified. Even when starting from Voltaren® Emulgel®, A36 did not provide any evidence of an effect, since the comparison did not relate exactly to the composition of Voltaren® Emulgel®. The problem had to be defined as an alternative, and the solution was obvious in view of D1, D2 and D4.

Appellant 02 also considered D1 as the closest prior rather than Voltaren® Emulgel®. However, even when starting from Voltaren® Emulgel®, the problem could be at best the provision of a formulation providing an improved skin permeation. There was a reasonable expectation of success that the incorporation of oleyl alcohol would provide this technical effect, in view of D2. A27 provided further arguments why the salt form of diclofenac had no incidence on an increase of skin permeation. Moreover, the compositions disclosed in D1 and D2were very close to the compositions as claimed, and the skilled person would have associated the teaching of Voltaren® Emulgel® to these documents.

Admission of auxiliary requests 1-4 into the proceedings

According to the appellants, auxiliary requests 1 and 4 were not part of the first instance proceedings. They should have been brought forward during first instance. At the present stage of the proceedings, they were late filed and add complexity to the case.

Auxiliary requests 1-3 - Inventive step

No further arguments were provided.

Auxiliary request 4 - Inventive step

According to appellant 01, the tests in A36 did not provide a comparison with the claimed formulation. The formulation tested in A36 differed from the composition in claim 1 of auxiliary request 4 in the amounts of carbomer, diethylamine, and water. There was no evidence on file that the composition of auxiliary request 4 led to an improvement based on the

differentiating features over Voltaren® Emulgel® 1.16%. The solution was obvious, for the same reasons as discussed in connection with the main request.

XII. The arguments of the respondent may be summarised as follows

Admission of documents A34 and A36 into the proceedings

These documents were filed in reply to the statements of grounds of appeal and related to the assessment of inventive step.

Main request - Inventive step

Voltaren® Emulgel® was the closest prior art, since it also related to an emulsion-gel and was in fact the starting point of the invention. Both the qualitative and the full quantitative composition of Voltaren® Emulgel® had been publicly available at the priority date; the qualitative composition was known from D8, and the quantitative composition was publicly available from A33. Said quantitative composition of Voltaren® Emulgel® did not change over the time, as highlighted by A35.

The distinguishing features between Voltaren® Emulgel® and the invention of the opposed patent were:
- the amount of the active ingredient (feature a) and
- the presence of 0.5-2% of a specified fatty alcohol (feature b).

The effects associated with the distinguishing features resulted in surprising benefits. The patent showed in tables 1-3 the results of a higher in vitro skin permeation. Table 4 of the patent showed that lauryl

alcohol, myristyl alcohol and stearyl alcohol also had a higher in vitro cumulative permeation on human skin. Furthermore, the compositions of the invention had proven to be physically and chemically stable.

The benefits of the claimed topical pharmaceutical composition could therefore be summarized as follows:
(A) High skin permeation
(B) Very low systemic absorption
(C) Essentially no irritation on human skin after administration
(D) Chemical and physical stability
(E) Full dissolution of diclofenac diethylammonium salt, and
(F) Higher pain relief.

Tables 1-4 and test examples 1 and 2 of the patent, as well as A36, clearly supported the presence of the above effects (A), (D) and (E).

The objective technical problem could therefore be formulated as being the provision of a stable topical pharmaceutical composition in the form of an opaque emulsion-gel comprising diclofenac diethylammonium and having (A) a higher skin permeation, resulting in a longer lasting pain relief and a reduced dosing frequency, without compromising (B) systemic absorption, (C) irritation on human skin after administration, (D) chemical and physical stability, and (E) the full dissolution of diclofenac in the formulation.

The objective technical problem was solved by a formulation according to the claims, using in particular an amount of 2-4% (w/w) of diclofenac diethylammonium salt in combination with 0.5-2% (w/w)

of a saturated or unsaturated C10-C18 fatty alcohol. This was shown by the examples of the contested patent and by the experiments A36. With regard to A36, the differences between the composition of Voltaren® Emulgel® and the composition according to the invention tested in A36 lay in adjustments linked with the maintenance of the viscosity of the composition.

The solution was not obvious, since there was no hint to modify the commercial product Voltaren® Emulgel® by increasing the amount of DDEA to 2-4% (w/w) and by including 0.5-2% (w/w) of a saturated or unsaturated C10-C18 fatty alcohol selected from the group consisting of stearyl alcohol, myristyl alcohol, lauryl alcohol and oleyl alcohol, while leaving the other components unchanged.

In particular, the skilled person would not have combined Voltaren® Emulgel® and D2, which aimed to provide a topical, local or systemic effect of diclofenac sodium in a different form, namely a simple monophasic gel, while the claimed invention was directed to an opaque emulsion-gel with a different, less polar and non-interchangeable salt of diclofenac. Emulsion-gels were a delicate formulation format due to their biphasic nature and any alteration in form of adding or omitting any component(s) could have unpredictable repercussions on multiple characteristics. The skilled person would therefore not have consulted D2.

There was no hint or indication in D1 that the incorporation of stearyl alcohol, myristyl alcohol, lauryl alcohol or oleyl alcohol in the amount of 0.5-2% (w/w) was somehow beneficial. The same considerations applied for D4 and A4'.

Therefore, claim 1 was non-obvious and hence involved an inventive step.

Admission of auxiliary requests 1-4 into the proceedings

All these requests were a response to the statement of grounds of appeal and had to be admitted.

Claim 1 of auxiliary request 1 was based on the claims of the Main Request and previous Auxiliary Request 3 as submitted in the first instance proceedings.

Auxiliary request 2 corresponded to auxiliary request 3 as submitted in the first instance proceedings and auxiliary request 3 corresponded to auxiliary request 4 from the first instance proceedings.

Auxiliary requests 1-3 - Inventive step

Auxiliary Request 1 further distanced the claimed invention from the teaching of D1 and focused more strongly around the test examples exemplifying the invention.

The amendments made to claim 1 of auxiliary requests 2 and 3 had been implemented in view of the attacks by both appellants starting from Example 2 of D1 in order to further distance the claimed invention from the teaching of D1.

Auxiliary request 4 - Inventive step

The claimed formulation corresponded to the formulation of example 1 and to the commercial product on the

market. Claim 1 was a unique combination of features providing an enhanced permeation, a good stability, a full dissolution of the active agent, without skin irritation. The problem was the provision of a formulation providing an enhanced permeation while maintaining the state of all other properties. The skilled person would not have been motivated to make five modifications to obtain the claimed formulation. The additional modifications necessary to arrive at the claimed subject-matter were not obvious for a skilled person starting from Voltaren® Emulgel®. The skilled person would not have been motivated to modify so many parameters to obtain a formulation with the same properties and there was no pointer in the prior art for this combination of features.

XIII. Requests

The appellant 01 (opponent 01) requested that the decision under appeal be set aside and that the patent be revoked. They also requested that documents A34 and A36, as well as auxiliary requests 1 and 4 not be admitted into the proceedings.

The appellant 02 (opponent 02) requested that the decision under appeal be set aside and that the patent be revoked. Additionally, they requested that auxiliary requests 1 to 4 not be admitted into the proceedings.

The respondent (patent proprietor) requested that the appeals be dismissed, alternatively that the decision be set aside and that the patent be maintained on the basis of one of auxiliary requests 1 to 4 filed with letter of 16 April 2020.

Reasons for the Decision

1. Admission of documents A34 and A36 into the proceedings

These documents were filed by the respondent in its reply to the statements of grounds of appeal, hence at the earliest stage of the appeal proceedings.

A34 is a declaration relating to the composition of Voltaren® Emulgel®, with a link to the online database for approved drugs in Sweden, and an e-mail relating to the practice of the Swedish Medical Product Agency before 2007. Said link and e-mail show the public availability of the formulation of the commercial product Voltaren® Emulgel®, and its exact qualitative and quantitative composition.

A36 relates to comparative tests between the commercial product Voltaren® Emulgel® and a formulation according to the invention. The data provided in A36 relate to the skin permeation of diclofenac and are a confirmation and a complement to the data presented in the contested patent, in particular in view of the Figures provided. As such, A36 cannot be seen as presenting a new or surprising information.

Both documents relate to the assessment of inventive step and constitute a response to the appellants' arguments and a reaction to the decision of the opposition division as regards the choice of the closest prior art and the demonstration of a technical effect. The composition of Voltaren® Emulgel® and the existence of an effect were indeed important points debated during oral proceedings in opposition proceedings.

The documents have therefore been filed in response to questions raised during the opposition proceedings, these questions still being relevant in the appeal proceedings, and also to complete informations already presented in the opposition proceedings.

Consequently, the Board admits these documents into the appeal proceedings (Article 12(4) RPBA 2007).

2. Main request -Inventive step

2.1 The invention concerns topical formulations of diclofenac diethylammonium salt (DDEA) in emulsion-gel form, presenting similar advantages as the commercial product Voltaren® Emulgel®, with improved efficiency, in particular as regards skin penetration and stability over time (see par. [0001]-[0007] of the patent specification).

2.2 The opposition division considered that D1 was the closest prior art which was preferred over D16 and the commercial product Voltaren® Emulgel® of D8.

Appellants 01 and 02 also consider D1 as the closest prior art art, in view of the disclosure of its examples 1 and 2.

The respondent considers the public prior use of Voltaren® Emulgel® as the closest prior art, on the basis of the disclosure of documents D8, A33 and A35.

The Board shares the respondent's opinion in view of the number of features in common.

2.2.1 The qualitative composition of Voltaren® Emulgel® is given in the document "Rote Liste 2007", namely D8. D8 discloses the following qualitative information with regard to the composition of Voltaren® Emulgel®:

(a) DDEA (1.16% by weight),
(b) no fatty alcohol,
(c) water,
(d) 2-propanol,
(e) propylene glycol (1,2-propanediol),
(f) acrylic polymer,
(g) paraffin and an ester of fatty alcohol and caprylic and capric acid,
(h) cetomacrogol,
(i) diethylamine.

The full qualitative and quantitative composition of Voltaren® Emulgel® was furthermore publicly available and was accessible via the Swedish Medical Products Agency, which entered the quantities of all active ingredients and all excipients of the commercial products in its database before November 2007. This is mentioned in document A33 filed by appellant 02, and confirmed in the declaration A34 filed by the respondent which explains the practice in Sweden before 2007. A34 gives furthermore the link where the information could be accessed via the online database for approved drugs in Sweden. As further indicated in A34, the qualitative and quantitative composition of registered medicaments was available until November 2007 to companies subscribing to the pharmacovigilance service. After November 2007, only the qualitative information was available to third parties.

Hence, since a marketing authorization for Voltaren® Emulgel® was granted in Sweden in 2005, the full

quantitative composition of Voltaren® Emulgel® has been publicly available in Sweden from 2005 to 2007, i.e. before the priority date of the opposed patent.

The public availability of the qualitative and quantitative composition of Voltaren® Emulgel® is directly confirmed by the disclosure of document A33. A33, which refers to this Swedish database, is a post-published "Scientific Advice", dated March 3, 2009 and was delivered from the Spanish Medicines Agency to appellant 02. A33 discloses in Table 1 at page 5 the full quantitative composition of Voltaren® Emulgel® in comparison to the commercial product Diclofenac Kern Pharma 1% Emulgel from appellant 02.

A33 discloses the following quantitative and qualitative information with regard to the composition for Voltaren® Emulgel®:

a) 1.16% w/w DDEA
b) no fatty alcohol
c) about 65% w/w water
d) 20% w/w isopropanol
e) 5% w/w propylene glycol (1,2-propanediol)
f) 1.2% w/w of carbomer 934P
g) 5% w/w of a lipid phase of paraffin and cococaprylate/capric (Cetiol)
h) 2% w/w of a non-ionic surfactant (polyoxyethylene alkyl ether)
i) 0.9% w/w of diethylamine.

This composition is confirmed by the declaration A35, submitted by the respondent, which provides the following information in respect to Voltaren® Emulgel® having a pH comprised between 7 and 8 :

a) 1.16% w/w DDEA
b) no fatty alcohol
c) 64.64% w/w water
d) 20% w/w isopropyl alcohol
e) 5% w/w propylene glycol
f) 1.2% w/w Carbopol 934P
g) 5% w/w of Cetiol LC (Caprylic/capric acid fatty alcohol ester) and liquid paraffin heavy
h) 2% w/w Cetomacrogol 1000 (polyoxyethylene 20 cetyl ether)
i) 0.9% w/w of diethylamine
j) 0.1% w/w perfume crème.

Said document A35 indicates furthermore that in 2001, the composition of Voltaren® Emulgel® was modified once by the replacement of Carbopol 934P by the same amount of Carbopol 974P, and that before that and since 2001, no variations have been composed on the type and amounts of ingredients of Voltaren® Emulgel®.

Consequently, it has convincingly been shown on the basis of the disclosure of D8, A32, A33, A34 and A35 that the quantitative and qualitative composition of Voltaren® Emulgel® was publicly available and known before the priority date of the contested patent and also that said composition was qualitatively and quantitatively constant over time. This point was not disputed by the appellants during the oral proceedings.

The distinguishing features between the claimed subject-matter and the composition of Voltaren® Emulgel® are therefore:

a) the amount of DDEA which is 1.16% by weight in Voltaren® Emulgel® and 2-4% by weight in claim 1.

b) and the presence of 0.5-2.0% by weight of a C10-C18 fatty alcohol selected among lauryl alcohol, myristyl alcohol, stearyl alcohol and oleyl alcohol.

2.3 According to the appellants, the problem is the provision of an alternative topical formulation of DDEA.

According to the respondent, the problem is the provision of an opaque emulsion-gel comprising DDEA and having a) a higher skin permeation, resulting in a longer-lasting pain relief and a reduced dosing frequency, without compromising b) systemic absorption, c) irritation on human skin after administration, d) chemical and physical stability and e) the full dissolution of diclofenac in the formulation.

2.4 As a solution to these alleged problems, claim 1 of the main request proposes a formulation comprising in particular DDEA in an amount of 2-4% by weight and the presence of 0.5-2.0% by weight of a C10-C18 fatty alcohol selected among lauryl alcohol, myristyl alcohol, stearyl alcohol and oleyl alcohol.

2.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect, in particular as defined by the respondent.

2.5.1 Table 1 of the contested patent shows the cumulative permeation of Voltaren® Emulgel® compared *inter alia* to a formulation presented as similar to Voltaren® Emulgel® but nevertheless unspecified, and comprising 2.32 wt% of DDEA and 2 wt% of oleyl alcohol. The cumulative skin permeation of diclofenac is 2.76 fold higher after 24 hours with the composition according to the invention comprising oleyl alcohol.

This result is confirmed in Tables 2 and 3 of the contested patent, which show the same comparison of Voltaren® Emulgel® with formulations of examples 1a, 1 and 1b comprising 2.32 wt% of DDEA and respectively 0.5, 0.75 and 1.0 wt% of oleyl alcohol. All the formulations according to the invention show an increase of the skin permeation of diclofenac of at least 2.4 fold until 3.0 fold after 24 hours.

Test examples 1, 2 and 3 of the contested patent show furthermore that the emulgel (emulsion-gel) of example 1 demonstrates a good stability of the active substance and of the emulgel, as well as a good skin tolerance, without however providing a comparison with the commercial product Voltaren® Emulgel®.

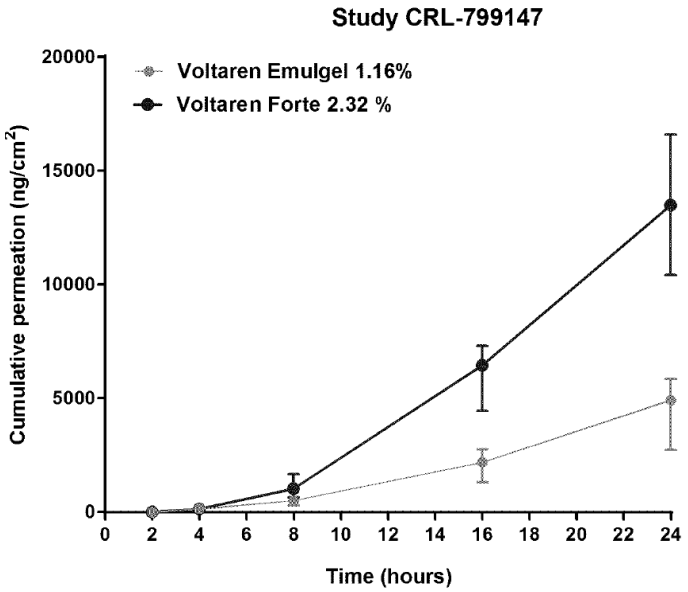
2.5.2 The respondent provided document A36 to demonstrate and confirm the existence of a technical effect. Said document shows two studies comparing the effects on skin permeation of the application of 20 mg (Test CRL-799147) or 10 mg (Test CRL-799388) of Voltaren® Emulgel® and a corresponding composition comprising 2.32% of DDEA and oleyl alcohol.

As pointed out by appellant 01, the composition comprising 2.32% of DDEA and oleyl alcohol had several other minor differences over the composition of Voltaren® Emulgel®, namely the amount and quality of carbomer, and the amounts of diethylamine and isopropanol. These minor differences were convincingly justified by the respondent by the necessity to make an adjustment of the composition, in view of the presence of oleyl alcohol and of greater amounts of DDEA, and of the maintenance of the viscosity of the composition by adjusting the amounts of carbomer, diethylamine and

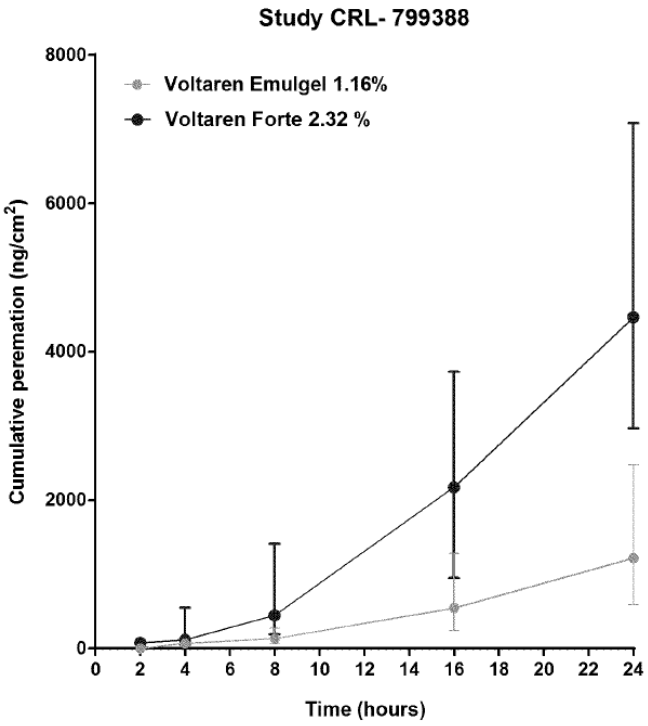
isopropanol to obtain the same level of viscosity as the commercial product Voltaren® Emulgel®.

The studies disclosed in A36 show a more than 3-fold increase in human skin penetration of DDEA when given in the composition comprising oleyl alcohol as illustrated by following Figures 1 and 2 of A36:

- Figure 1:



- Figure 2:



Consequently, the disclosure of document A36 proves in an explicit and convincing way that the presence of oleyl alcohol increases the skin penetration of DDEA, independently from the other excipients, and in a proportion higher than the difference in concentration of DDEA in the compositions.

2.5.3 In view of this evidence, the problem appears to be as defined by the respondent, and the Board is also convinced that the claimed composition presents an improvement in skin permeation over the closest prior-art compositions, without compromising systemic absorption, irritation on human skin after administration, chemical and physical stability and the full dissolution of diclofenac in the formulation, so that the problem is credibly solved.

2.6 Obviousness

As to obviousness, documents D2 and D1 were in particular mentioned by the appellants.

2.6.1 D2 discloses the use of oleyl alcohol as a skin permeation enhancer for diclofenac sodium, to be used in a transdermal aqueous gel composition having topical, local or systemic effect (see D2, page 5, 2nd par.). The concentration of oleyl alcohol is comprised between 0.75 and 3% and is preferably 1.5% by weight, hence in the same concentration range as in claim 1 of the main request (see D2, page 5 last par.- page 6 first par., page 7, 4th par. and examples 1-3). D2 mentions that the use of a combination of 0.75 to 3 wt%, e.g 1.5wt%, of oleyl alcohol and of 15 to 60 wt%, e.g 30 wt%, of isopropyl alcohol allows the obtention of a clear gel, that is chemically and physically stable, has a local or systemic effect and does not produce irritation in the skin (see D2, page 6, 2nd par., page 7 4th par.).

Example 4 of D2 provides a comparison of the cumulative skin permeation after 24 hours between *inter alia* the commercial gel Voltaren®, and an aqueous gel of diclofenac sodium without oleyl alcohol, which are respectively 39.22 µg/cm^2 and 25.54 µg/cm^2; said cumulative skin permeation values of both products are however much lower than another disclosed commercial gel comprising also 1.16 wt% of DDEA, namely Oxagel®, which has a cumulative skin permeation of 106.44 µg/cm^2 after 24 hours.

Example 4 explains that a diclofenac sodium gel does not reach the permeation rates obtained with commercial formulations, in view of the higher polarity of the

molecule of diclofenac sodium compared with that of DDEA, the less polar molecule being more permeable through the *stratum corneum*. Said example shows also implicitly the importance of the formulation of the composition for the skin permeation of diclofenac, in view of the different results obtained by respectively Voltaren® and Oxagel® which comprise both the same salt of diclofenac, i.e.DDEA, at a concentration of 1.16 wt%.

Example 5 of D2 shows that the addition 0.75 wt%, 1.5 wt% or 3.0 wt% of oleyl alcohol to a gel comprising diclofenac sodium enhances very strongly the skin permeation of diclofenac, going from a skin permeation of diclofenac sodium without oleyl alcohol of 25.54 µg/cm^2 to values of 1272.86 µg/cm^2, 1511.83 µg/cm^2 and 936.91 µg/cm^2 with respectively 0.75 wt%, 1.5 wt% and 3.0 wt% of oleyl alcohol. These results clearly confirm that oleyl alcohol is a strong skin permeation enhancer for diclofenac.

The results of examples 4 and 5 illustrate the general teaching of D2, which is that one of the most suitable and best permeation enhancer to be used in a transdermal gel composition comprising diclofenac sodium is oleyl alcohol (see D2, page 5. lines 9-30). As shown by the experiments of examples 4 and 5, the presence of oleyl alcohol as permeation enhancer appears indeed to be a major determinant of the skin permeation of diclofenac, in particular a much greater determinant of skin permeation than the salt form of diclofenac and even the gel formulation, in view of the much lower results obtained by respectively Voltaren® and Oxagel®.

In view of the general teaching of D2 and of the results shown in example 5 for the skin permeation of the sodium salt of diclofenac in the presence of oleyl alcohol, the skilled person would be strongly incited to test and use oleyl alcohol as skin permeation enhancer in other compositions comprising diclofenac, even if diclofenac is present in said other compositions in the form of a different salt. If oleyl alcohol has such a high impact on the skin permeation of a polar salt of sodium diclofenac, the skilled person would indeed also strongly expect to have such effect on a less polar or more hydrophobic salt of diclofenac, such as DDEA, even if this effect would not necessarily be present in the same proportions.

The use of oleyl alcohol as skin permeation enhancer for a composition comprising DDEA, such as in Voltaren® Emulgel®, appears therefore to be obvious for the skilled person.

2.6.2 The incorporation of oleyl alcohol in an emulgel instead of a gel as disclosed in D2, can furthermore not be seen as a technical obstacle or as a factor of instability of the emulgel, as argued by the respondent, in particular in view of the teaching of D1.

D1 discloses in examples 1 and 2 emulgels of DDEA which have a very similar composition as Voltaren® Emulgel® and the composition as claimed in the main request. D1 mentions that the presence of a solvent, i.e an alcohol, and of a co-solvent, i.e. PEG or propanediol, acts as skin permeation enhancer (see D1, col. 3, l. 49- col. 4, l. 9).

Example 1 of D1 discloses the following composition:

a) 1.16% w/w DDEA
b) no fatty alcohol
c) about 65% w/w water
d) 20% w/w isopropyl alcohol
e) 3% of PEG 300
f) 1% w/w Carbopol 934P
g) 5% w/w of Cetiol LC (Caprylic/capric acid fatty alcohol ester) and paraffin
h) 2% w/w Cetomacrogol 1000 (polyoxyethylene 20 cetyl ether)
i) 0.7% w/w of diethylamine to a pH which is not given.

Example 2 of D1 discloses the following composition:

a) 1.16% w/w DDEA
b) no fatty alcohol
c) about 60% w/w water
d) 20% w/w isopropyl alcohol
e) 10% w/w of propanediol
f) 1,2% w/w Carbopol 934P
g) 5% w/w of Cetiol LC (Caprylic/capric acid fatty alcohol ester) and paraffin
h) 0.9% w/w Cetomacrogol 1000 (polyoxyethylene 20 cetyl ether)
i) 0.7% w/w of diethylamine to a pH which is not given.

The teaching of D1 envisages the addition of fatty alcohols such as lauryl alcohol, myristyl alcohol, stearyl alcohol or oleyl alcohol as constituent of the lipid phase of the emulgel, in a concentration range of 3 to 15 wt% (see D1, claim 1 and col. 4, l. 27-37). D1 does not link these compounds with an improved skin permeation but teaches clearly that the addition of a fatty alcohol such as oleyl alcohol in the lipid phase of an emulgel is a normal design option to be considered by the skilled person and that it cannot be

considered as a factor of instability of the emulgel. The argument of the appellant is therefore not convicing and cannot be followed.

2.6.3 The choice of a higher concentration range of DDEA than in Voltaren® Emulgel® , namely 2-4% by weight, is also an option that the skilled person would reasonably consider in view of the teaching of D1, which shows that such concentration range of DDEA is compatible and possible with the emulgels disclosed therein.

D1 discloses indeed a range of concentration of the active substance such as DDEA in its emulgel comprised between 1 and 5 wt% (see claims 1, 13 and 14). The solvent and co-solvent system used in the emulgels disclosed in D1 is furthermore qualitatively and quantitatively identical to the one used for the claimed invention (see D1, col. 3, l. 49-col. 4, l. 9). D1 teaches in particular that the function of the co-solvent, which is preferably also a polyethylene glycol or propylene glycol in an amount of 5-10 wt%, is to maintain the active ingredient left behind on the skin in solution (see claim 1 and col. 3, l. 66-67). In view of this technical teaching, the choice of a concentration range of 2-4 wt% of DDEA in an emulgel is an option that the skilled person would consider and is also considered as obvious.

2.6.4 The solution of a formulation comprising in particular DDEA in an amount of 2-4% by weight in claim 1 and the presence of 0.5-2.0% by weight of a C10-C18 fatty alcohol selected among lauryl alcohol, myristyl alcohol, stearyl alcohol and oleyl alcohol of claim 1 of the main request is therefore obvious in view of the teaching of documents D2 and D1.

2.7 Consequently, the main request does not meet the requirements of Article 56 EPC.

3. Admission of auxiliary requests 1-4 into the proceedings

The auxiliary requests were filed with the reply to the statements of grounds of appeal, and thus at the earliest possible time in the appeal proceedings. They are a reaction to the arguments presented by the appellants in their statements of grounds of appeal. Moreover, auxiliary requests 2 and 3 correspond to auxiliary requests 3 and 4 filed during the opposition proceedings on 18 June 2018. Thus, the Board does not see any reason not to admit these requests into the appeal proceedings (Article 12(4) RPBA 2007).

4. Auxiliary requests 1-3 - Inventive step

The independent claim 1 of these requests do not comprise any further distinguishing feature over Voltaren® Emulgel®, since all the amendments have been made in view of D1 as closest prior art. Hence, the 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 requests 1-3.

Auxiliary requests 1-3 do therefore not meet the requirements of Article 56 EPC.

5. Auxiliary request 4 - Inventive step

5.1 Claim 1 of auxiliary request 4 is based on example 1 of the application as filed, and its subject-matter

presents further distinguishing technical features over Voltaren® Emulgel® which are as follows:
- the presence of 17.50 wt% of isopropanol, instead of 20 wt% isopropanol in Voltaren® Emulgel®,
- the presence of 1.70 wt% of Carbomer 980, instead of 1.2 wt% of carbomer 934P in Voltaren® Emulgel® ,
- the presence of 1.35 wt% of diethylamine, instead of 0.9 wt% of diethylamine in Voltaren® Emulgel®.

The claimed composition comprises also some minor changes, such as the presence of 64.26 wt**%** of purified water instead of 65 wt% of water in Voltaren® Emulgel®, and the presence of butylhydroxytoluene, and perfumes.

5.2 According to the respondent, the problem remains the provision of an opaque emulsion-gel comprising DDEA and having a) a higher skin permeation, resulting in a longer-lasting pain relief and a reduced dosing frequency, without compromising b) systemic absorption, c) irritation on human skin after administration, d) chemical and physical stability and e) the full dissolution of diclofenac in the formulation.

5.3 In the Board's view, the adaptation or adjustments of amounts or nature of the excipients in a formulation represent routine tasks for the person skilled in the art.

In the present case, the adaptation of the amounts of isopropanol or diethylamine and the choice of the nature and amount of carbomer constitute normal design options that the skilled person would consider in view of the solubilisation of the active substance, the stabilisation of the composition, or the adjustment of its rheological properties. The same argumentation has also been presented by the respondent to justify the

adjustments made to the comparative composition presented in the experiments A36, wherein minor modifications were made to obtain an adequate level of viscosity of the product used as equivalent to Voltaren® Emulgel®.

Consequently, the additional modifications necessary to arrive at the claimed subject-matter are obvious for a skilled person starting from Voltaren® Emulgel®.

Auxiliary request 4 does not meet the requirements 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:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated