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Datasheet for the decision of 16 November 2021

Case Number: T 0280/19 - 3.3.07

Application Number: 12700406.7

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IPC: A61K9/06, A61K47/10, A61P5/26, A61K31/568, A61K31/58, A61K9/00

Language of the proceedings: EN

Title of invention:
TESTOSTERONE FORMULATIONS

Patent Proprietor:
Ferring BV

Opponent:
Müller Fottner Steinecke Rechtsanwalts- und Patentanwaltspartnerschaft mbB

Headword:
Testosterone formulations/FERRING

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Admission of a document (Yes)
Main request - Amendments (Yes)
Main request - Inventive step (Yes)

Decisions cited:
T 0337/95

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Case Number: T 0280/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 November 2021

Appellant: (Opponent)	Müller Fottner Steinecke Rechtsanwalts- und Patentanwaltspartnerschaft mbB P.O. Box 11 40 Römerstrasse 16b 52428 Jülich (DE)
Representative:	Witthoff Jaekel Steinecke Patentanwälte PartG mbB Postfach 1140 52412 Jülich (DE)
Respondent: (Patent Proprietor)	Ferring BV Polaris Avenue 144 2132 JX Hoofddorp (NL)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 November 2018 rejecting the opposition filed against European patent No. 2667851 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 667 851 was granted on the basis of a set of 19 claims.

Independent claim 1 as granted read as follows:

"1. A transdermal or transmucosal formulation comprising:
- 2% wt of testosterone,
- C_2 to C_4 alkanol,
- polyalcohol, and
- monoalkyl ether of diethylene glycol,
wherein said formulation comprises fatty alcohols, fatty acids, and fatty esters having a branched or linear acid moiety having 8 or more carbon atoms or having a branched or linear alcohol moiety having 8 or more carbon atoms in a total amount of less than 0.1 % wt."

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

III. The appeal of the opponent lies from the decision of the opposition division to reject the opposition.

IV. The documents cited during the opposition proceedings included the following:
D1: Percutaneous penetration enhancers, Springer-Verlag Berlin Heidelberg 2015; Chapter 9: Fatty Alcohols, Fatty Acids, and Fatty Acid Esters as Penetration Enhancers; Babu et al.
D2: WO 2004/080413 A2
D3: Pharmacokinetics made easy - 11 - Designing dose regimens; D.J. Birkefl (Aust Prescr 1996; 19:76-8 Jul 1996 DOI: 10.18773/austprescr. 1996.069)
D4: Safety and efficacy of testosterone gel in the treatment of male hypogonadism; Lakshman and Basaria (Clinical Interventions in Aging 2009:4 397-412)
D5: WO 2005/039531 Al
D6: WO 99/24041
D7: US 2004/0044086 Al
D8: WO 2006/027278 Al
D9: M. Brunner et al. Br. J. Clin. Pharmacol., 71(6), 852-859 (2011)
D10: In vitro skin permeation of estradiol formulations (IVP Study 1276/17, dated 27-10-2017 by Ferring Pharmaceuticals).
D11: In vitro skin permeation of testosterone formulations (IVP Study 1291/18, by Ferring Pharmaceuticals).

V. According to the decision under appeal, document D11 was admitted into the proceedings.

The requirements of Article 123(2) EPC were fulfilled and the skilled person was given sufficient technical advice in the specification as to how to carry out the invention over the whole breadth of the claims.

The subject-matter of claims 1-19 of the patent was novel over D2.

As regards inventive step, the closest prior art was D2, and the distinguishing feature between the subject-matter of claim 1 and the disclosure of D2 was the amount of testosterone of 2 wt% instead of 1 or 1.25 wt%. In view of the effect shown in examples 3 and 6 of the patent and in D11, the problem to be solved was the provision of a transdermal/transmucosal testosterone formulation having more regulated testosterone plasma levels with a more steady therapeutic effect. The solution was not obvious in view of D2 or D6. The same conclusion would have applied when starting from D5 as closest prior art.

VI. The opponent (hereinafter the appellant) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal the appellant submitted the following items of evidence:
D12: Pharmacology, Rang et al, 1995, pages 92-93
D13: US2003/0199426 A1.

VIII. With its reply dated 7 August 2019, the patent proprietor (hereinafter the respondent) filed auxiliary requests 1 to 4.

IX. A communication from the Board, dated 1 March 2021, was sent to the parties. In it the Board expressed its preliminary opinion that D11 was part of the appeal proceedings, that the requirements of Article 123(2) EPC were met by the main request, and that the available experimental data demonstrated the presence of improved pharmacokinetic properties for the claimed formulation over the formulations of the closest prior art D2.

X. With a letter dated 19 July 2021, the appellant informed the Board and the respondent that it will not attend the oral proceedings. In a communication issued on the 15 September 2021, the Board informed the parties that the oral proceedings to be held on 21 September 2021 were cancelled.

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

Admission of D11 into the appeal proceedings

The opposition division (OD) decided that Dll was *prima facie* relevant since it responded to a point raised in the OD's preliminary opinion. The OD's conclusion in this regard however ensued from an incorrect approach.

Main request - Amendments

There was no disclosure in the application as filed of the feature that the formulation comprises long-chain fatty alcohol, long-chain fatty acids and long-chain fatty esters in a total amount of less than 0.1 wt. %. This feature was not considered to be equivalent to "substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty acid esters". Given the "open language" used in the definition of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters, there was no clear and unambiguous basis for the exclusion in claim 1 of just the fatty acids, fatty alcohols and fatty esters having 8 or more carbon atoms in the acid or alcohol moiety. Reference was also made to decision T 337/95.

Main request - Inventive step

In the decision, the OD used D2 as closest prior art. At least D5 and D7 could also be selected as the closest prior art.

The only feature that could be held to distinguish the subject-matter claimed from the disclosure of D2 was the (relative) amount of testosterone of 2 wt.% instead of 1 wt.% or 1.25 wt.% or as a selection from the 0.01-10 wt.% range.

According to example 3 of the patent, the 2 wt.% testosterone gel resulted in higher permeation and higher transdermal flux whereas the results of example 6 pointed in the opposite direction. A technical problem might be regarded as being solved only if it was credible that substantially all claimed embodiments exhibit the technical effects upon which the invention is based.

The objective technical problem was to be formulated as providing a testosterone formulation that allowed for a reduction of the gel volume needed to apply a given testosterone dose to the skin of a subject. For compositions closely resembling those of example 6, the objective technical problem might be formulated as providing a testosterone formulation that allowed for a reduction of the gel volume needed to apply a given testosterone dose to the skin of a subject while maintaining acceptable pharmacokinetic properties.

The solution was obvious and the claimed subject-matter was not inventive.

If document D5 was considered as the closest prior art, the considerations in an inventive step analysis starting from D5 would be largely the same as for D2. Hence, the arguments presented above regarding D2 equally applied.

D7 constituted an equally promising springboard as D2 and D5, and the claimed subject-matter lacked inventive merit vis a vis the combined teachings of D7 (as the closest prior art) and D2.

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

Admission of D11 into the appeal proceedings

D11 was an experimental report that included comparative test data and was filed by the patent proprietor two months before the date of the hearing, within the term set by the opposition division under Rule 116(1) EPC . The opponent requested not to admit D11 into the proceedings for the first time in the course of the hearing. The OD's reasons for admitting D11 into the proceedings, especially its prima facie relevance for the decision, were set out in its decision and resulted in a reformulation of the objective technical problem, a finding of inventive step and, ultimately, maintenance of the patent as granted. The appellant had not presented any arguments to support the assertion that the OD had incorrectly exercised its discretion when admitting D11 into the proceedings, and the OD had evidently applied the correct principles when deciding on the admittance of D11 into the proceedings, namely considering whether it was prima facia relevant.

Main request - Amendments

The original claim wording "wherein said formulation is substantially free of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters" was amended and the amendment was based on the disclosure of the paragraph bridging pages 9 and 10 of the application as filed.

Main request - Inventive step

D2 was the closest prior art and the formulation of claim 1 of the patent in suit differed from the formulations known from D2 in the concentration of testosterone. The technical effect resulting from this difference was an improvement in the pharmacokinetic properties as shown in example 3 of the patent, and further supported by D11. The in vivo study of example 6 thus represented a further comparison with the closest prior art. The technical problem could be defined as the provision of a transdermal or transmucosal formulation comprising testosterone as the active ingredient and having improved pharmacokinetic properties. The solution was not obvious in view of D2 and D6.

With regard to the choice of the closest prior art, D2 was closer to the patent in suit than D5 or D7, so that D5 or D7 could not be regarded as an equally valid starting point.

XIII. Requests

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

also requested that document D11 not be admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed, alternatively that the patent be maintained according to the sets of claims filed as auxiliary requests 1-4 with letter of 7 August 2019. The respondent also requested that the appellant's request not to admit D11 into the proceedings be rejected.

Reasons for the Decision

1. Admission of D11 into the proceedings

The experimental data D11 was filed on 10 August 2018 which was the final day for making submissions under Rule 116 EPC, eight weeks before the oral proceedings before the opposition division which took place on 10 October 2018.

D11 was considered to be *prima facie* relevant for the decision, since it contained data relating to the skin permeation of formulations according to the invention. The experimental data of D11 was discussed during the oral proceedings before the opposition division and was an explicit part of the decision as regards inventive step.

The Board considers this document to form part of the appeal proceedings as the decision of the opposition division is based in part on that document and D11 has been relied on by the respondent in its reply to the grounds of appeal. Furthermore, in the Board's view the opposition division appears to have exercised its

discretionary power according to the right principles and in a reasonable way.

2. Main request (patent as granted)- Article 123(2) EPC

2.1 According to the appellant, there is no disclosure in the application as filed of the feature "wherein said formulation comprises fatty alcohols, fatty acids, and fatty esters having a branched or linear acid moiety having 8 or more carbon atoms or having a branched or linear alcohol moiety having 8 or more carbon atoms in a total amount of less than 0.1 % wt" included in claim 1 of the main request. The reason is that the application as filed related to a composition "substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty acid esters", which does not equate to the feature "compris[ing] fatty alcohol, fatty acids, and fatty esters... in a total amount of less than 0.1 wt.%".

2.2 Claim 1 as originally filed (see WO2012/101016 A1, hereinafter the application) relates indeed to a composition "substantially free of long-chain fatty alcohols, long chain fatty acids, and long-chain fatty esters".

The description as originally filed defines on page 9, line 31 to page 10, line 2 what is meant by long-chain fatty alcohols, acids or esters, namely "*Long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters* as used herein should be understood to encompass fatty alcohols and fatty acids having a branched or linear carbon body having 8 or more carbon atoms, and esters thereof, i.e. fatty esters having a branched or linear acid moiety having 8 or more carbon

atoms or having a branched or linear alcohol moiety having 8 or more carbon atoms."

The description on page 10, lines 4-6 further explains that "*substantially free of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters* as used herein should be understood to mean comprising fatty alcohols, fatty acids and/or fatty esters in a total amount of less than about 0.1 %wt."

Hence, in view of these disclosures, the skilled person would link the disclosed percentage of less than about 0.1 %wt to the specifically disclosed long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters; the use of the term "moiety" is also directly disclosed in the passage of page 9 quoted above.

The subject-matter of claim 1 is therefore disclosed directly and unambiguously in the application as filed and the main request meets the requirements of Article 123(2) EPC.

2.3 The appellant cited decision T 337/95 in support of its objection under Article 123(2) EPC.

This decision was however about Article 84 EPC and not about Article 123(2) EPC, and constitutes furthermore a justification in favour of the respondent of the amendments brought to claim 1 of the main request. In this decision it was explained that the expression "lower alkyl" did not have a generally accepted meaning and therefore was not suitable to clearly define the meaning of the group R1. The applicant's first auxiliary request in which R1 was limited to methyl was allowed by the Board.

For similar reasons the appellant replaced the feature "substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty esters", by the feature "wherein said formulation comprises fatty alcohols, fatty acids, and fatty esters having a branched or linear acid moiety having 8 or more carbon atoms or having a branched or linear alcohol moiety having 8 or more carbon atoms in a total amount of less than 0.1 % wt". Consequently, the amendment was justified to avoid a lack of clarity of the claim.

3. Main request - Inventive step

3.1 The invention relates to transdermal or transmucosal formulations of testosterone, that delivers therapeutically effective amounts of testosterone in a controlled manner, has high skin tolerability, efficient and regulated skin absorption, and enables daily doses having lower volumes and thus shorter administration regimens (see specification, par. [0001] and [0007]).

3.2 D2 was considered by the opposition division to be the closest prior art. The appellant also considers D5 or D7 to constitute suitable starting points for the assessment of inventive step.

3.2.1 D2 discloses topical compositions comprising a steroid for treating hormonal disorders, comprising in particular a delivery vehicle comprising a C_2 to C_4 alkanol, a polyalcohol and monoalkyl ether of diethylene glycol or a tetraglycol furol, and is free of long chain fatty alcohols or long chain fatty acids to prevent the formation of unpleasant odors (see D2, page 8, lines 10-19, page 9, lines 1-4). Said composition is in particular adapted for testosterone,

which can be present in a concentration comprised between 0.01 and 10 wt% , in particular 1% by weight, as shown in Tables 2, 4 and 5 below (see D2, pages 19 and 20):

Table 2

Testosterone	0.01% -10%
Carbomer	0.05%-4%
Triethanolamine (adjust to pH 5.9)	0.05%-1%
Alcohol	20%-65%
Propylene glycol	1%-15%
Diethylene glycol monoethyl ether	1%-15%
Ion Exchange Purified Water q. ad.	20%-65%

Table 4

Testosterone	0.01%-10%
Carbomer 980	1.2%
Triethanolamine (adjust to pH 5.9)	0.4%
Alcohol	46.28%
Propylene glycol	6%
Diethylene glycol monoethyl ether	5%
Disodium EDTA	0.06%
Ion Exchange Purified Water q. ad.	100%

Table 5

Testosterone	1%
Carbomer 980	1.2%
Triethanolamine (adjust to pH 5.9)	0.4%
Ethanol	47.5%
Propylene glycol	6%
Diethylene glycol monoethyl ether	5%
Disodium EDTA	0.06%
Ion Exchange Purified Water q. ad.	100%

D2 discloses furthermore in example 2 a topical gel comprising testosterone 1 %w/w, diethylene glycol

monoethyl ether 5.00 %w/w, propylene glycol 6.00 %w/w, ethanol 47.52 %w/w, carbomer 1,20 %w/w, triethanolamine 0.35 %w/w, disodium EDTA 0.06 %w/w and water 38.87 % w/w. Example 1 shows a composition comprising 1.25 %w/w of testosterone, without diethylene glycol monoethyl ether.

A concentration of 2 wt% of testosterone is therefore not directly disclosed in D2.

3.2.2 D5 discloses a transdermal or transmucosal pharmaceutical formulation comprising an active ingredient and a solvent system including a monoalkyl ether, a glycol, as well as mixture of alcohol and water. Examples 3-6 and 8-11 show gel compositions comprising 1% w/w of testosterone, said compositions being similar to the compositions disclosed in D2. The considerations as regards inventive step would therefore be the same as for D2, and the Board does not see any reason to consider D5 as a separate piece of closest prior art for this reason.

3.2.3 D7 relates to topical gels comprising from 0.01 to 10 weight% of an androgenic steroid, preferably 2-3 weight% (see par. [0018]), in particular testosterone, in a composition comprising propylene glycol and ethanol; said compositions may also comprise a further resorption improver, such as ethoxydiglycol, which appears to be a synonym for diethylene glycol monoethyl ether (see [0031] or [0051]).

Some compositions of D7 are disclosed in the following Table:

TABLE 1

	G-I	G-II	G-III	L-I	L-II	L-III
Testosterone	2.5	2.5	1.0	2.5	2.5	1.0
α-bisabolol	1.0	—	—	1.0	—	—
Lecithin	1.5	—	—	1.5	—	—
Ethanol (96%)	51.5	56.0	56.0	51.5	56.0	56.0
Propylene glycol	5.0	5.0	5.0	5.0	5.0	5.0
Carbopol 980	1.0	1.0	1.0	—	—	—
Tromethamol	0.14	0.14	0.14	—	—	—
water	37.36	35.36	36.86	38.5	36.5	38.0

A specific composition with a concentration of 2 wt% of testosterone and with diethylene glycol monoethyl ether is not disclosed in D7.

3.2.4 In view of the above, document D2 appears to be the closest prior art. This conclusion was anticipated by the Board in its communication of 1 March 2021 to which the appellant did not reply.

3.3 According to the appellant, the problem is the provision of a testosterone formulation that allows for a reduction of the gel volume needed to apply a given testosterone dose to the skin of a subject. For compositions closely resembling those of example 6, the appellant defines the problem as the provision of a testosterone formulation that allows for a reduction of the gel volume needed to apply a given testosterone dose to the skin of a subject while maintaining acceptable pharmacokinetic properties.

According to the respondent, the problem is the provision of a transdermal or transmucosal formulation comprising testosterone and having improved pharmacokinetic properties.

3.4 The patent in suit provides several examples providing a comparison between a gel composition comprising 1 wt% of testosterone (hereinafter T1) and a gel composition comprising 2 wt% of testosterone (hereinafter T2).

Experiments D11 were also filed by the respondent to show the existence of an effect.

3.4.1 In example 3, T1 and T2 are tested in an in vitro model, at **identical gel volumes** per cell, hence T2 is tested at a higher total amount of testosterone per cell and per cm2. The results shown in Figures 3B-8B show that a higher drug instant flux is obtained with T2 (Batch 4 in the Figures) in comparison to T1 (Batch 3 in the Figures).

The cumulated drug permeated is higher for T2 in comparison to T1 in Figures 3A, 4A and 6A, while it is the contrary in Figures 5A, 7A and 8A. Said results are given in percentage (%) as indicated in the Figures and in Table 5 of example 3, whereas in paragraph [0021] or Figure 9 of the patent they are expressed in in µg/cm2.

In example 4, three formulations were tested in vitro:
- 10 mg gel of T1 (hereinafter 10-T1)
- 20 mg gel of T1 (hereinafter 20-T1)
- 10 mg gel of T2 (hereinafter 10-T2).

The results shown in Figure 9 show that 10-T2 has a superior skin permeation of testosterone than 10-T1, but less than 20-T1.

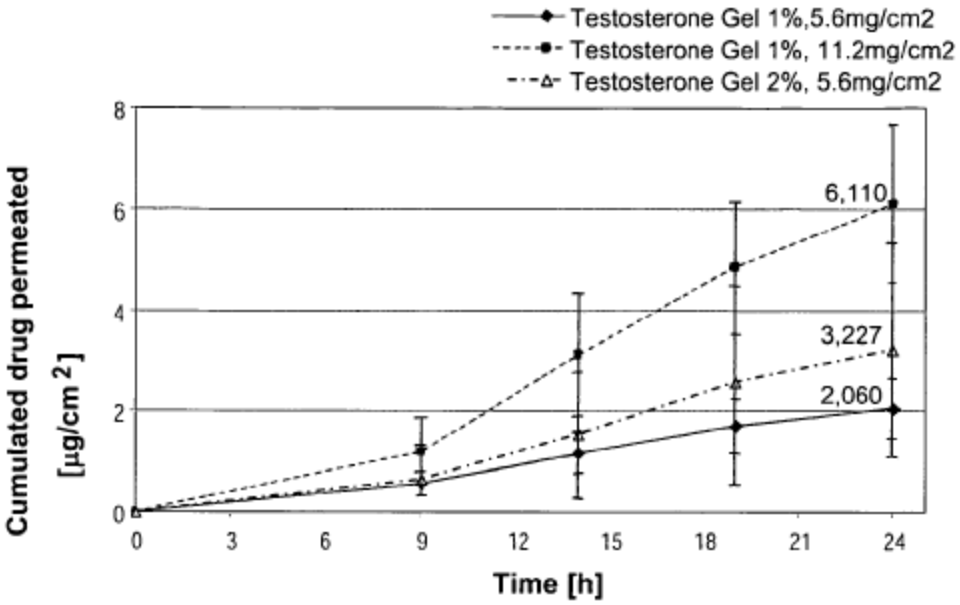


FIG. 9

Figure 10 shows that for 10-T2, the maximum drug instant flux is reached later and is not characterized by the rapid increase observed with 20-T1, or with 10-T1.

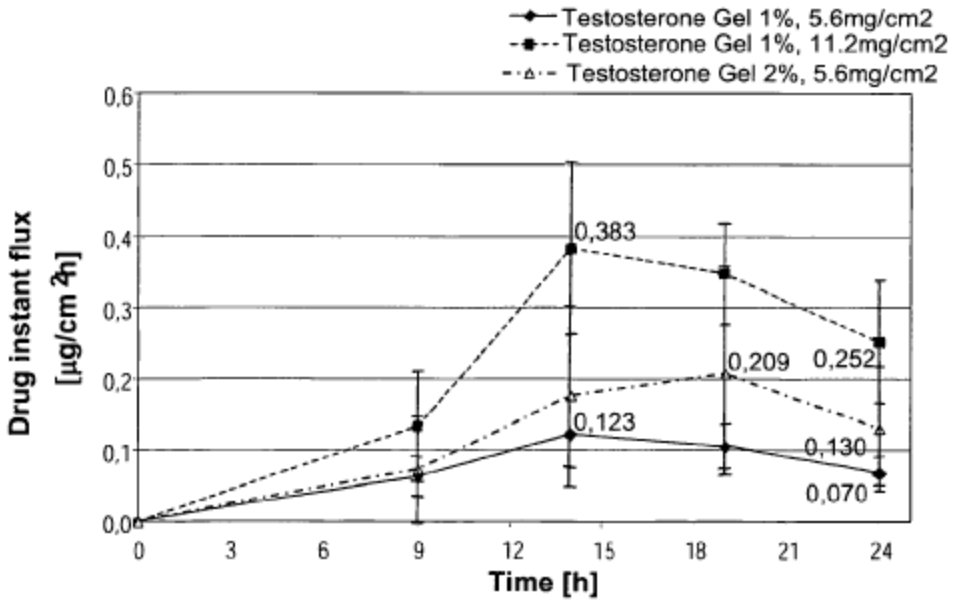


FIG. 10

In example 6, the same compositions comprising 1 wt% and 2 wt% testosterone (T1 and T2) were compared *in vivo*, with **identical testosterone dosages or amounts** applied to identical skin surfaces, i.e. gel volumes providing 50 mg of testosterone in both cases were applied to 1000 cm2 of skin, namely 5-T1 and 2.5-T2 (5 g of T1 and 2.5 g of T2).

The total AUC was 6691.38 ng.hr/dL and a Cmax of 602.3 ng/dL for T1 and 4822.54 ng.hr/dL and a Cmax of 316.9 ng/dL for T2. The testosterone plasma levels are given in Figure 12.

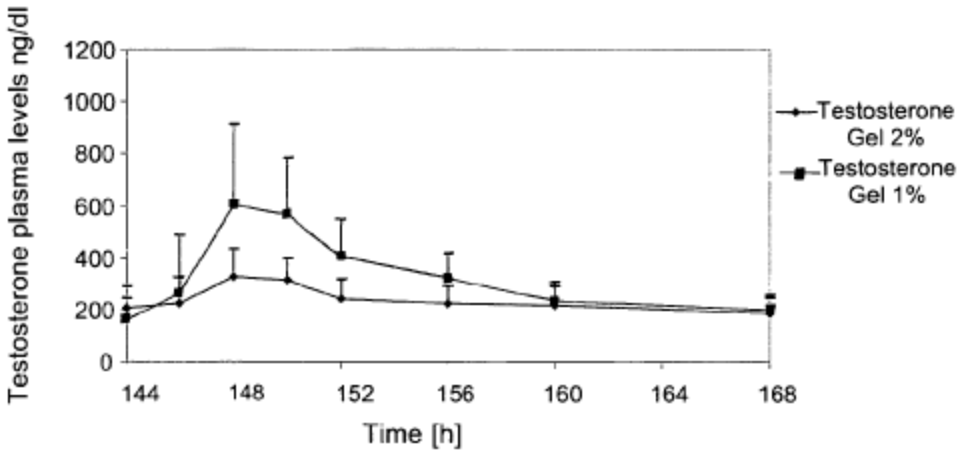


FIG. 12

Figure 12 shows that T2 provides more sustained and controlled plasma levels, with less C_{max} values and a less relative variability, hence a more steady therapeutic effect, resulting in less side effects than with T1 (see the specification par. [0135]-[0138]).

In the experiments D11, two identical composition comprising 1 wt% or 2 wt% (T1 and T2) were tested in vitro in **an amount of 10 mg each**. T1 provided a higher relative cumulative delivery than T2 (14.65 % vs 12.22

%), while the mean cumulative delivery was slightly higher for T2 (14.46 mg/cm2 vs 8.98 mg/cm2); the steady-state flux was significantly higher for T2 over T1 (0.64 µg/cm2h for T2, 0.44 µg/ cm2h for T1). The detailed results with regards to the cumulative delivery were as follows:

Table 3. Testosterone cumulative delivery after 24h permeation

Formulation	Applied amount of formulation	Replicates	Mean absolute cumulative delivery [µg/cm²±SD]	Mean relative cumulative delivery [%±SD]	Steady-state flux [µg/cm²h]
D2-1159-080-01A	10 mg	9	14.46 ± 6.12	12.22 ± 4.95	0.64 ± 0.20
D2-1159-081-01A	10 mg	9	8.98 ± 4.64	14.65 ± 6.99	0.44 ± 0.15

Figure 1. In vitro cumulative relative delivery of Testosterone

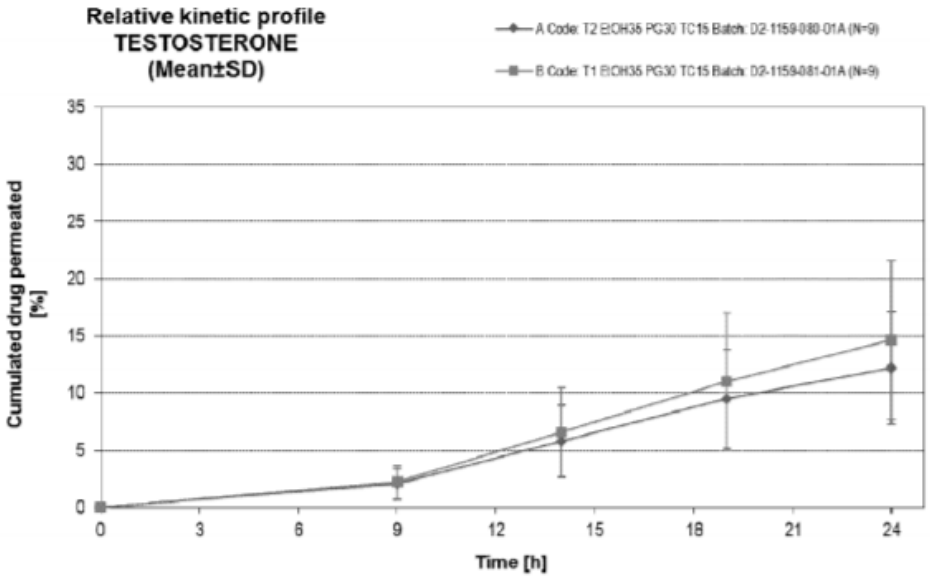
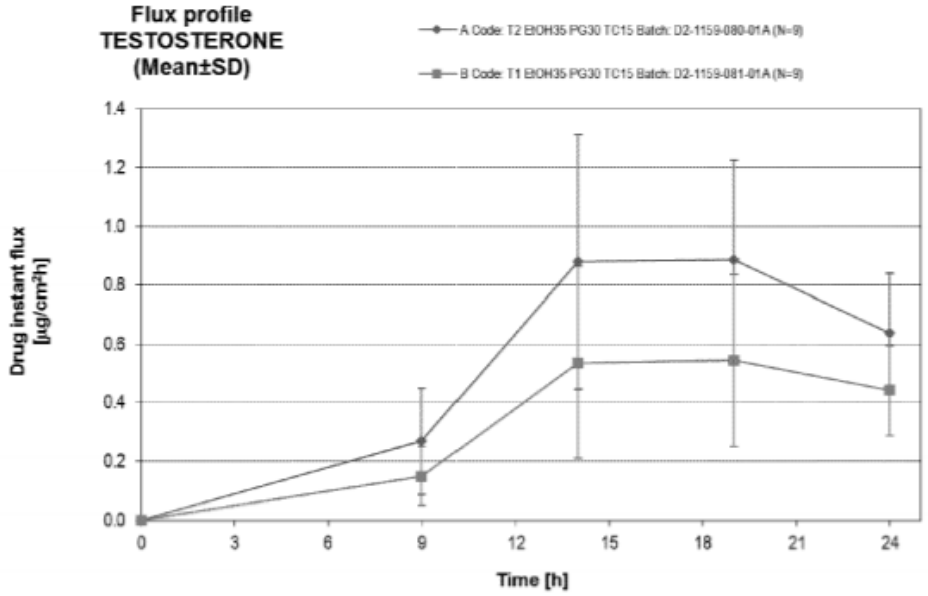


Figure 2. In vitro flux profile of testosterone



3.4.2 In view of these experiments, the following can be concluded:

(a) The experiments of examples 3, 4 and 6 of the contested patent and the experiments D11 provide a comparison between a composition comprising 1 wt% of testosterone and a composition comprising 2 wt% of testosterone. These comparisons appear to be valid and show the existence of a technical effect due to the only distinguishing feature between the subject-matter of claim 1 of the main request and document D2.

(b) There does not appear to exist a contradiction between the results of examples 3 and 6 as argued by the appellant. Figure 10 shows that, when administered **at equivalent volume**, T2 has a higher skin permeation than T1, as also shown in Example 3. It is only when T1 is administered **at equivalent**

dose or amount that the skin flux appears to be superior to the skin permeation of T2.

(c) When administered **at identical gel volumes**, T2 provides a higher drug instant flux than T1, but both T1 and T2 have a close relative cumulative delivery (see Fig. 3A-8A, 3B-8B). These results are confirmed by the experiments D11. Figure 9 of the patent shows that T2 provided a superior skin permeation of testosterone compared to T1 when keeping the same gel loading per unit area.

As argued by the respondent, due to the higher instant flux linked with T2 when administered **at identical gel volumes** than T1, the administration of testosterone through T2 can be reduced, while the total amount of testosterone can be maintained; example 7 shows that, in order to achieve equivalent plasma levels, 5.4 grams of T1 are needed, instead of 3.7 grams of T2.

(d) When administered **at identical dosages or amounts**, such as 20-T1 and 10-T2 in example 4, or 2.5-T2 and 5-T1 in example 6, T1 has a superior skin permeation and a drug instant flux than T2 (see Figures 9 and 10). This is confirmed by the in vivo tests of example 6, which show a higher AUC and C_{max} with the administration of a given dosage of T1 in comparison to the administration of the same dosage of T2 (see Figure 12). Examples 4 and 6 appear to provide concordant results.

However, the results of Example 6 and Figure 10 show that when T1 and T2 are administered **at identical dosages**, T2 provides a more sustained and

controlled release, with in particular a reduced peak plasma concentration.

With T2, the maximum drug instant flux is reached later than with T1 in any dose amount (around 18 hours instead of around 14 hours, cf. Fig 10), and is not characterized by the rapid increase observed for the same amount of testosterone when administered as T1.

It is thus credible that the administration of testosterone through T2 allows a more steady concentration within the therapeutic window and minimizes the possible side effects. A formulation comprising testosterone according to the claimed invention has indeed improved pharmacokinetic properties.

3.5 Consequently, the problem appears to be as defined by the respondent i.e. the provision of a transdermal or transmucosal formulation comprising testosterone and having improved pharmacokinetic properties. As underlined above, this conclusion is based on experiments in which the gels compared differ only in the testosterone concentration. Thus, these experiments are suitable to demonstrate the effects arising from the different concentration of testosterone. In the absence of any evidence or convincing technical argument from the side of the appellant that could cast doubt on the experimental data discussed above, the Board agrees with the conclusion of the opposition division that the results of this experimental evidence can be extrapolated over the whole scope of the claim (see point 6.3 of the decision).

3.6 With regard to obviousness, the appellant cited documents D2, D3, D4, D5, D6, D7 and D12.

3.6.1 In the first place, the appellant also argued that a higher testosterone concentration appears to be a logical approach if the skilled person wished to lower the volume of gel to apply.

However, this consideration does not take into account of the definition of the technical problem. Furthermore, when it comes to lowering the volume of gel to apply, a logical approach could also be to administer the gel in multiple doses of lower volume instead of one dose of high volume, as it is done for instance in D2 (see for instance example 6 and corresponding Figures 3D-3F).

Moreover, when increasing the testosterone concentration in a given formulation, one would a priori have expected a corresponding increase in the drug flux and, thus, a more rapid increase in the plasma level. This is however the opposite of what was observed in the present case, since the drug flux decreases and is more steady with T2 than with T1 at the same dosage.

3.6.2 D2 suggests a testosterone concentration comprised between 0.01 and 10% by weight with a strong pointer to a concentration of 1% by weight when diethylene glycol monoethyl ether is present (see Table 5 or examples 2-4). An alternative formulation comprising 1.25% by weight of testosterone is also disclosed in D2, but in a different composition without diethylene glycol monoethyl ether (see example 1). The general purpose of D2 is to provide a sufficient permeation enhancement to steroid drugs such as testosterone or estradiol, and

there is no concern in this document to improve the pharmacokinetics. The selection of a testosterone concentration of 2% by weight to improve the pharmacokinetic properties, i.e. to allow a more steady concentration and a minimization of the side effects is therefore not obvious in view of the disclosure of document D2.

3.6.3 D3 was cited by the appellant to show that, based on common general knowledge, the skilled person would reasonably expect that an increase in testosterone concentration would be likely to reduce the transdermal absorption rate. This document is however about dosage regimens and relates mainly to intravenous administration, and for this reason appears to be irrelevant for the present case; it does not appear possible to draw any conclusion from this document as to the incidence of the concentration of any active agent in a transdermal or transmucosal composition on its pharmacokinetic properties.

3.6.4 D4 is a review article about transdermal testosterone gels explaining the issue of skin transfer of residual testosterone, which would, according to the appellant, motivate the skilled person to reduce the volume of gel needed to apply a given therapeutic testosterone gel product and recognize that a higher testosterone concentration would be a logical approach to lower the volume of gel to apply (see D4, page 408). The passage cited by the appellant however mentions solely that "in men, the bioavailability of applied testosterone is limited to 10%-15%" and said passage does not suggest any particular formulation or concentration of testosterone in gel formulations. This teaching is not related to the claimed solution and cannot render the claimed solution obvious. Moreover, D4 does not provide

any relevant teaching in relation to the technical problem defined in point 3.5 above.

3.6.5 D5 discloses transdermal compositions for minimizing skin residues and inhibiting or delaying crystallization of the active agent, by the use of a combination of monoalkyl diethylene glycol and a glycol at specific ratios. Examples 3-6 show transdermal compositions with 1 wt.% of testosterone, and there is no further suggestion to modify the concentration of testosterone. The selection of a testosterone concentration of 2% by weight to improve the pharmacokinetic properties is therefore not obvious in view of the disclosure of document D2.

3.6.6 D6 relates to compositions for topical drug application comprising a penetration-enhancing system providing a reduced skin irritation. This penetration enhancing system is different from the formulation of the present invention and comprises in particular oleic acid, which is excluded by the subject-matter of claim 1 of the main request, an alcohol and a glycol. D6 discloses gel formulations containing testosterone in an amount of 2 wt.% (examples 5 and 9).

Starting from D2, the skilled person would have no reason to consider D6, in view of the different penetration enhancement system used, in particular the use of oleic acid in the formulations disclosed therein. D6 is also silent about the more sustained and controlled plasma levels observed for 2 wt.% testosterone containing formulations. Consequently, no motivation is derivable for the skilled person from D2 in combination with D6 to formulate gels without oleic acid and to simultaneously increase the concentration to 2% with the aim of solving the technical problem.

The combination of D2 and D6 therefore cannot render obvious the claimed solution.

D7 relates to a gel composition comprising testosterone, preferably in a concentration from 2 to 7 wt.%. The examples of D7 show a concentration of testosterone of 2.5 or 1 wt.%. D7 determines the serum concentration of testosterone over time (see Figure 1), but the optimization of the serum or plasma concentration with reduced or minimized plasmatic peaks for avoiding potential side effects is not addressed in D7. D7 teaches the administration of the gel for 10 minutes followed by immediate washing it off to avoid a possible contamination by another person (see par. [0015] and [0067]); this way of administration which is close to a bolus administration provides an additional penetration enhancement, with a high increase in the testosterone concentration in the blood, leading to a normalization of the hypogonadel values (see par. [0015]). Accordingly, there is no motivation or incentive in D7 as regards a potential solution to the problem of providing a controlled plasma level with reduced or minimized plasmatic peaks of testosterone; there is also no suggestion in D7 to adjust the concentration of testosterone to 2 wt.% for this purpose. The claimed solution is not obvious in view of D2 in combination with D7.

D12 is a common general knowledge document about different kinetic models and dealing with oral and intravenous administration. It provides a very general teaching with regard to the rate of absorption and plasma concentration, which is not relevant for the present case.

3.7 The subject-matter of claim 1 of the main request is not obvious and the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob A. Usuelli

Decision electronically authenticated