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Datasheet for the decision of 22 June 2018

Case Number: T 1038/14 - 3.3.01

Application Number: 01270333.6

Publication Number: 1343508

IPC: A61K31/565, A61P5/24

Language of the proceedings: EN

Title of invention:
USE OF AN OESTROGEN IN THE MANUFACTURE OF A COMPOSITION CONTAINING OESTROGEN FOR THE TREATMENT OF ATROPHIC VAGINITIS

Patent Proprietor:
Novo Nordisk Health Care AG

Opponents:
Laboratorios Léon Farma, S.A.
Helm AG

Relevant legal provisions:
EPC Art. 113(1), 100(b), 54, 56
EPC R. 103(1)(a), 111(2)
RPBA Art. 11

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It can be changed at any time and without notice.

Keyword:

Right to be heard - substantial procedural violation (yes) - decision under appeal insufficiently reasoned
Reimbursement of appeal fee - (yes)
Remittal to the department of first instance - special reasons for not remitting the case
Grounds for opposition - insufficiency of disclosure (yes) - main request
Novelty - second (or further) medical use (yes)
Inventive step - (no)

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Case Number: T 1038/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 22 June 2018

Appellant: (Patent Proprietor)	Novo Nordisk Health Care AG Thurgauerstrasse 36/38 8050 Zürich (CH)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Party as of right: (Opponent 1)	Laboratorios Léon Farma, S.A. Pol. Ind. Navatejera C/La Vallina s/n 24008 Villaquilambre, Leon (ES)
Representative:	Schön, Christoph Dr. Schön, Neymeyr & Partner mbB Bavariaring 26 80336 München (DE)
Appellant: (Opponent 2)	Helm AG Nordkanalstrasse 28 20097 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 April 2014 concerning maintenance of the European Patent No. 1343508 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 1 343 508 was granted with eight claims. Claims 1 and 4 read as follows:

"1. The use of an oestrogen in the manufacture of a tablet composition containing oestrogen for the treatment of atrophic vaginitis in a woman wherein from 9 to 11 µg estradiol are to be administered twice weekly."

"4. The use according to any one of the preceding claims, furnishing a reduced risk of osteporosis [sic]*."*

II. Two 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. In the course of the opposition proceedings, the patent proprietor submitted an amended main request and three auxiliary requests.

Claim 1 of the amended main request reads as follows:

"1. The use of an oestrogen in the manufacture of a tablet composition containing oestrogen for the treatment of atrophic vaginitis in a woman wherein from 9 to 11 µg estradiol are to be administered vaginally twice weekly."

Claim 1 of the first auxiliary request reads as follows:

"1. The use of an oestrogen in the manufacture of a tablet composition containing oestrogen for the treatment of atrophic vaginitis in a woman wherein from 9 to 11 µg estradiol are to be administered vaginally twice weekly and wherein the treatment is preceded by a pre-treatment which is a daily treatment with the same dose of estradiol as that used in the twice weekly treatment."

Dependent claim 4 in both the main request and first auxiliary request reads as follows:

"4. The use according to any one of the preceding claims, furnishing a reduced risk of osteoporosis."

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

D2: Maturitas 14, 23-31 (1991)

D5: Maturitas 15, 121-127 (1992)

D6: Acta Obstet Gynecol Scand 79, 293-297 (2000)

D9: Vagifem® information for patients (version of February 2000 and revised version of July 2003)

D13: Menopause 5(4), abstracts P-16 to P-18 (1998)

V. The decision under appeal is the interlocutory decision of the opposition division, announced on 4 February 2014 and posted on 4 April 2014, rejecting the patent proprietor's main request and finding that the patent as amended in the form of the first auxiliary request met the requirements of the EPC.

VI. In the decision under appeal, the opposition division came, *inter alia*, to the following conclusions:

There were serious doubts that a therapeutic benefit could be achieved over the entire scope covered by the definition of the treatment of atrophic vaginitis in the claims of the main request, which merely required the twice-weekly vaginal administration of from 9 to 11 µg estradiol. All the examples provided in the patent specification included a pre-treatment or "induction" phase during which the same dosage was administered daily for two weeks, prior to the twice-weekly regimen. Several prior-art documents, likewise disclosing an induction phase, lent further support to the opponents' argument that no treatment benefit could be achieved without an induction phase. Hence, maintenance of the patent on the basis of the claims of the main request was prejudiced on the ground under Article 100(b) EPC.

The amendments made in the first auxiliary request met the requirements of Articles 123(2) and 84 EPC. Claim 1 included a mandatory pre-treatment phase. The claimed subject-matter was disclosed in a manner sufficiently clear and complete, since the skilled person would be able to implement the pre-treatment without undue burden (Article 100(b) EPC).

Document D13 related to a pharmacokinetic study investigating the systemic absorption of vaginally applied estradiol in post-menopausal women. However, the document was silent on its efficacy as a topical treatment against atrophic vaginitis. The other prior-art documents cited in the proceedings either did not disclose the same dose and dosage regimen as specified in claim 1 or did not disclose tablets. Hence, none of them anticipated the subject-matter

of claim 1 of the first auxiliary request (Articles 100(a), 52(1) and 54 EPC).

Starting from the teaching of documents D2 or D6, deemed to represent the closest prior art, the objective technical problem was the provision of an improved vaginal treatment of atrophic vaginitis which offered the same therapeutic benefits as the product used according to those documents (Vagifem®) but reduced the systemic absorption of estradiol and thereby the risk of clinically relevant systemic side effects. Since document D2 stated that 25 µg of estradiol ("E2" or "17β-oestradiol" in D2) twice a week was the lowest effective dose for the long-term treatment of post-menopausal atrophic vaginitis, the person skilled in the art would not have considered administering the lower doses specified in claim 1 of the first auxiliary request. Nor did any other prior-art documents clearly teach doing so. Thus, the claimed subject-matter involved an inventive step (Articles 100(a), 52(1) and 56 EPC).

VII. The patent proprietor, opponent 1 and opponent 2 each filed an appeal against that decision. For the sake of simplicity, the parties will continue to be referred to as "patent proprietor" and "opponents" in this decision.

VIII. The patent proprietor requested the reversal of the opposition division's decision and the maintenance of the patent on the basis of the existing main request (see point III above). In response to the opponents' appeals, the patent proprietor submitted five sets of claims as auxiliary requests.

IX. In their written submissions, both opponents requested that the patent proprietor's appeal be dismissed and, in addition, that the decision under appeal be set aside and that the patent be revoked. Opponent 2 requested that it be reimbursed for the appeal fee, owing to a substantial procedural violation.

X. By letter of 12 June 2018, opponent 1 withdrew its appeal and announced that it would not be attending the oral proceedings scheduled by the board. It did not provide any further arguments or modified requests.

XI. Oral proceedings before the board were held on 22 June 2018 in the absence of opponent 1, in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

XII. At the start of the oral proceedings, the patent proprietor submitted four amended sets of claims (main request and first to third auxiliary requests) to replace all pending claim requests. The amendments made consisted of the withdrawal of two of the previous claim requests and the deletion of certain dependent claims in the remaining requests.

Claim 1 of the pending **main request** is identical to claim 1 of the former main request considered in the decision under appeal, and claim 1 of the pending **first auxiliary request** is identical to claim 1 of the former first auxiliary request considered in the decision under appeal (see point III above).

Claim 1 of the **second auxiliary** request reads as follows:

"1. The use of an oestrogen in the manufacture of a tablet composition containing oestrogen for the treatment of atrophic vaginitis in a woman wherein

10 µg estradiol are to be administered vaginally twice weekly and wherein the treatment is preceded by a pre-treatment which is a once daily treatment with 10 µg estradiol for two weeks."

Claim 1 of the **third auxiliary** request reads as follows:

"1. The use of an oestrogen in the manufacture of a tablet composition containing oestrogen for the treatment of atrophic vaginitis in a woman wherein 10 µg estradiol are administered vaginally once daily for two weeks, and subsequently 10 µg estradiol are administered twice weekly for more than two months."

XIII. The opponents' arguments may be summarised as follows:

Procedural violation and reimbursement of appeal fee

Opponent 2 argued that a substantial procedural violation had occurred. While the opposition division had concluded in the decision under appeal that the former first auxiliary request met the requirements of the EPC, the reasoning given was incomplete, since it did not address the pending objection of insufficiency of disclosure with regard to the feature "furnishing a reduced risk of osteoporosis", present in dependent claim 4 of that request.

Main request - sufficiency of disclosure

A pre-treatment phase (induction treatment) involving daily administration of the medication and preceding the regimen involving twice-weekly administration (maintenance treatment) was necessary to obtain the desired therapeutic effect. Contrary to the patent proprietor's reasoning, such pre-treatment was not an implicit limiting feature of claim 1. The efficacy of

the twice-weekly treatment with doses of 9 to 11 µg when not preceded by a pre-treatment phase (covered by the definition of the therapy plan in claim 1) was not rendered credible by the patent in suit, which provided only data obtained from trials involving a two-week pre-treatment phase.

First auxiliary request - novelty

It was evident from the title and from the paragraph "Conclusions" in document D13 (referring to "Treatment with E2 10 µg" and "treatment of atrophic vaginitis"), that the treatment of atrophic vaginitis had in fact been carried out during the study reported in D13. Also, the term "treatment" by itself implied the success of the treatment. According to D13 ("Results"), the amount of estradiol which was absorbed systemically had decreased in the period from first dose to week twelve of the 10 µg regimen, which meant that the treatment must have been effective in regenerating the vaginal epithelium. In any case, it would only make sense to determine the pharmacokinetic parameters addressed in D13 (relating to undesirable systemic absorption) if the efficacy of the topical dosages tested had first been established.

According to a different line of reasoning, efficacy of treatment was not a mandatory feature of claim 1 and therefore could not be used to establish novelty: Since the definition of the pre-treatment in claim 1 was rather general and unspecific, the claim also covered embodiments which would not be successful in treating atrophic vaginitis.

First auxiliary request - inventive step

If the board were to consider the subject-matter of this request novel, the assessment of inventive

step would have to be based on the assumption that the disclosure of document D13 differed from the subject-matter of claim 1 in not explicitly disclosing the efficacy of the 10 µg dosage regimen of estradiol in treating atrophic vaginitis. On that basis, the objective technical problem for the person skilled in the art consisted merely in verifying that the therapy plan using 10 µg doses did indeed provide a therapeutic effect in the treatment of atrophic vaginitis. The solution to that problem simply involved re-working the therapy plan already known from D13. In view of the disclosure in document D13 alone or combined with the technical teaching of document D5, the person skilled in the art would have expected a treatment using 10 µg doses to be successful.

Second and third auxiliary requests

Since the amendments made in claim 1 of each request did not add any further features distinguishing the claimed subject-matter from the disclosure of document D13, the arguments with regard to inventive step were the same as for the first auxiliary request.

XIV. The patent proprietor's arguments may be summarised as follows:

Main request - sufficiency of disclosure

Claim 1 of the main request was drafted to be directed to a second medical use and therefore, by definition, excluded non-working embodiments. Consequently, when the claim was properly construed in the context of the disclosure of the patent specification and of common general knowledge, the person skilled in the art, knowing that pre-treatment was required to achieve the therapeutic effect, would infer that the therapy plan must include a pre-treatment phase involving daily

administration of the medicament, without this being expressly stated in the claim. Since claim 1 therefore did not cover a use in which the manufactured tablet was to be administered in a therapy plan without a pre-treatment phase, the opponent's argument in that regard was irrelevant.

Furthermore, a person skilled in the art would have sufficient guidance for implementing the pre-treatment from the working examples provided in the patent specification and from common general knowledge.

It was not necessary for claim 1 to include the pre-treatment phase explicitly. According to the established case law of the boards of appeal, the primary function of a claim was to set out the scope of protection sought for an invention. To that end, the claim had to comprise the essential features of the invention, namely those which distinguished it from the closest prior art, but it was not necessary for the claim to identify all technical features or steps in detail. After all, the requirement of sufficiency of disclosure had to be met by the patent as a whole, not by a single claim.

First auxiliary request - novelty

Document D13 related only to pharmacokinetic data and did not disclose the treatment of atrophic vaginitis. In any case, the person skilled in the art could not have inferred from the information provided in D13 that the treatment involving the administration of 10 µg doses was effective in treating atrophic vaginitis. Contrary to the opponents' allegations, there was no direct correlation between a decrease in systemic absorption and therapeutic efficacy.

Auxiliary requests - inventive step

Document D2, which discussed treatment efficacy, provided a more suitable starting point for the assessment of inventive step than document D13, which was silent on the efficacy of the treatment. If the assessment of inventive step was nevertheless to start from the teaching of document D13, it had to be taken into account that claim 1 provided a treatment with the same benefit as the established regimen using 25 µg doses but also reduced the systemic absorption of estradiol. The objective technical problem was thus to provide an estradiol composition for the effective treatment of atrophic vaginitis which offered a therapeutic benefit combined with low systemic absorption, thereby lowering the risk of side effects. The person skilled in the art would have inferred from the prior art, in particular document D2 (page 30, lines 9 to 11), that 25 µg was the lowest effective dosage. There was no reasonable expectation that a therapy plan involving the administration of lower doses of 9 to 11 µg, as defined in claim 1, could provide the required therapeutic effect.

XV. The parties' final requests were as follows:

(i) The patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request or, in the alternative, of one of the first to third auxiliary requests, all filed during the oral proceedings on 22 June 2018.

(ii) Opponents 1 and 2 requested that the patent proprietor's appeal be dismissed, that the decision under appeal be set aside and that the patent be revoked. Opponent 2 further requested

that it be reimbursed for the appeal fee, owing to a substantial procedural violation.

Reasons for the Decision

The appeals of the patent proprietor and of opponent 2 comply with Articles 106 to 108 EPC and Rule 99 EPC and are therefore admissible.

1. Procedural violation and reimbursement of the appeal fee

1.1 The obligation under Rule 111(2) EPC to provide adequate reasoning in a decision open to appeal is closely linked to the principle of the right to be heard under Article 113(1) EPC, since the parties concerned have to be able to determine whether their objections and arguments were duly taken into account. A failure to provide such adequate reasoning is considered a substantial procedural violation justifying reimbursement of the appeal fee.

1.2 In its notice of opposition (see page 6 of the reasons), opponent 2 raised an objection of insufficiency of disclosure with respect to the requirement in dependent claim 4 of the opposed patent that the risk of osteoporosis was to be reduced by the use and treatment according to claim 1. In that context, the opponent argued that the patent in suit did not contain any evidence to show that the risk of osteoporosis could indeed be lowered by the treatment proposed.

1.3 The feature in question ("furnishing a reduced risk of osteoporosis") was also present, with identical wording, in claim 4 of the amended main request and of

the first auxiliary request filed during of the opposition proceedings (see point III above).

1.4 The objection to claim 4 is acknowledged in the decision under appeal (see page 10, point 13.2.2) as one of the objections to the main request pursuant to Article 100(b) EPC.

However, the main request is then refused under Article 100(b) EPC for other reasons, relating to the definition of the therapy plan in claim 1, without any discussion of the separate objection to claim 4 (see the decision under appeal, point 13.2.4).

When subsequently deciding, against the opponents, in favour of the first auxiliary request on the issue of Article 100(b) EPC, the opposition division does not discuss claim 4 or provide any reason why, in its opinion, its subject matter directed to a reduced risk of osteoporosis is adequately disclosed (see the decision under appeal: point 14.3.3, exclusively discussing the feature "pre-treatment" inserted into claim 1).

1.5 Since claim 4 is identically worded in the main request and the first auxiliary request, the objection to claim 4 is also valid for the first auxiliary request, and the issue should therefore have been addressed by the opposition division.

1.6 As a consequence, the reasoning in the decision under appeal as to why the first auxiliary request was deemed allowable is incomplete.

1.7 Under these circumstances, the board considers reimbursement of the appeal fee paid by opponent 2 to be equitable by reason of a substantial procedural violation (Rule 103(1)(a) EPC).

2. Remittal

2.1 Pursuant to Article 11 RPBA, a board shall remit a case to the department of first instance (Article 111(1) EPC) if fundamental deficiencies are apparent in the first-instance proceedings, unless special reasons present themselves for doing otherwise.

2.2 In the present appeal proceedings, none of the parties requested a remittal of the case. None of the patent proprietor's pending requests contain a claim corresponding to former claim 4. Moreover, considering that the application was filed on 13 December 2001 and the opposition proceedings started in August 2012, and that the board was in a position, based on the pending requests and the factual framework of the appeal, to reach a final decision without being obliged to examine a fresh case, remittal is not deemed necessary, or indeed appropriate when weighed against the interest of procedural economy.

3. Main request - sufficiency of disclosure

3.1 According to the established case law of the boards of appeal, where a therapeutic application is claimed in the form of the use of a substance for (or, as in the present case, "in") the manufacture of a medicament for a defined therapeutic application (known as the "Swiss-type" claim format), attaining the associated therapeutic effect is a functional technical feature of the claim.

Since the therapeutic effect is expressed in the claim, non-working embodiments are excluded from the scope claimed. However, if - irrespective of this functional restriction - the scope determined by the remaining mandatory technical features of such a claim also

covers non-working embodiments, there may be an issue of insufficient disclosure. Sufficiency depends on whether the person skilled in the art has the knowledge, or can obtain sufficient guidance from the specification, to be able to find appropriate working embodiments over the entire range determined by the remaining mandatory technical features, without undue burden.

3.2 In the present case, claim 1 of the main request defines, on the one hand, the therapeutic effect or indication (i.e. the treatment of atrophic vaginitis in a woman) and, on the other hand, the technical features of the medicament to be manufactured and the therapy plan for administering that medicament.

In view of the considerations mentioned in point 3.1 above, for the subject-matter of claim 1 to meet the requirement of sufficiency of disclosure, the patent in suit must disclose the suitability of the medicament to be manufactured for attaining the therapeutic effect when following the therapy plan defined in the claim. The following points must therefore be established:

(a) What are the mandatory technical features of claim 1 (including any implicit ones) with regard to the medicament and therapy plan?

(b) Do the mandatory technical features identified under point (a) suffice for attaining therapeutic efficacy in the treatment of atrophic vaginitis?

(c) If the question under (b) is answered in the negative, is the person skilled in the art given sufficient guidance (taking into account the information presented in the patent specification and common general knowledge) to find therapeutically efficacious embodiments over the

entire scope covered by the therapy plan for administering the medicament?

3.3 With regard to point (a), the therapy plan according to claim 1 mandatorily requires the twice-weekly vaginal administration of 9 to 11 µg estradiol, provided in tablets. It was in dispute between the parties whether a pre-treatment phase involving the daily administration of estradiol should be considered an implicit technical feature of the claim.

3.4 With regard to points (b) and (c), it was common ground between the parties that the topical administration of estradiol as a twice-weekly maintenance treatment must be preceded by induction therapy (i.e. pre-treatment) involving daily topical administration to ensure the therapeutic efficacy of the treatment of atrophic vaginitis, and that this was common general knowledge at the priority date of the patent in suit. Moreover, all examples presented in the patent in suit include such pre-treatment.

3.5 Thus, the decisive question is whether claim 1 is implicitly restricted to embodiments involving a pre-treatment phase, since the skilled person would have no guidance on how to achieve therapeutic efficacy without it (see points 3.2(a) and (c) and 3.3 above).

3.6 In that context, the patent proprietor argued that it was not necessary for a claim to identify all the technical features of an invention, but only those distinguishing it from the closest prior art. Upon a sensible reading of claim 1 taking into account common general knowledge, the person skilled in the art would understand that for the successful treatment of atrophic vaginitis by twice-weekly administration of estradiol as claimed, a pre-treatment phase involving

daily administration of the medication was needed, so as to prime the vaginal epithelium with estradiol. This understanding of claim 1 was further confirmed by the patent specification, in particular the working examples, which also involved a pre-treatment phase.

3.7 This argument cannot succeed, for the following reasons:

3.7.1 It is incorrect that only technical features distinguishing the claimed subject-matter from the closest prior art must be mentioned in a claim, and that any other features can be dispensed with. Rather, the technical features which must be mentioned are those necessary for the definition of the matter for which protection is sought (Article 84 EPC). As a rule, these include features which form part of the prior art as well as further features which distinguish the claimed subject-matter from the prior art (see Rule 43(1) EPC). By consulting the definition given in the claim, the skilled person must be able to establish which technical features are mandatory for the claimed invention.

3.7.2 Since a patent is presumed to describe and claim a new invention, the reader of a patent claim would not be in a position to know, or automatically assume, that certain features or steps known from the prior art or common general knowledge are mandatory in spite of their not being mentioned in the claim. The invention might simply not require those steps or features to be put into practice.

3.7.3 Claim 1 of the main request defines the twice-weekly vaginal administration of 9 to 11 µg estradiol in tablet form. Since the claim is clearly understandable in itself, there is no need for the reader to consult

the description or rely on common general knowledge in order to read further limitations into the claim which are not implicit in its wording.

3.7.4 Hence, if a pre-treatment phase was meant to be included as mandatory, it should have been indicated in the claim.

3.8 Contrary to the patent proprietor's argument, the dosage regimen defined in claim 1 does not therefore include a mandatory pre-treatment (or induction) phase which involves the daily topical administration of estradiol. Hence, the therapy plan according to claim 1 also covers embodiments without such a pre-treatment phase.

3.9 The patent in suit does not contain any information which might render it plausible that a therapy plan without a pre-treatment phase would provide therapeutic efficacy: and indeed, the patent proprietor explicitly stated that it was not arguing that that was the case.

3.10 For these reasons, the board concludes that the subject-matter of claim 1 of the main request is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art over the entire scope claimed (Article 100(b) EPC).

4. First auxiliary request - novelty

4.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that it additionally includes a pre-treatment phase which is a daily treatment with the same dose of estradiol as that used in the twice-weekly treatment.

As already mentioned (see points 3.1 and 3.2 above), the feature "for the treatment of atrophic vaginitis

in a woman" is a mandatory functional technical feature of claim 1 which involves attaining the specified therapeutic benefit. It must therefore be taken into account in the assessment of novelty and inventive step.

4.2 Document D13 is a conference abstract describing a study in which 58 post-menopausal women received vaginal tablets containing either 25 µg estradiol (Vagifem® 25 µg) or 10 µg estradiol for the topical treatment of atrophic vaginitis. The tablets were administered once daily for two weeks and then twice weekly for ten weeks, in a twelve-week randomised, double-blind parallel-group study (see D13: P-16, sections headed "Design" and "Conclusion").

4.3 D13 discloses only pharmacokinetic parameters relating to systemic absorption, but does not show any data relating to the efficacy of the topical treatment. Without such data, the reader is not in a position to infer that the therapy plan using the 10 µg dosage would achieve therapeutic efficacy in the treatment of atrophic vaginitis.

4.4 Contrary to the opponents' argument, the board considers that the data on systemic absorption disclosed in the "Results" section of D13 do not provide conclusive information regarding the efficacy of the treatment:

While D13 reports that, with the 10 µg dosage regimen, the amount of estradiol absorbed decreased in the period from first dose to week twelve, this was different with the 25 µg dosage regimen (Vagifem® 25 µg), for which an increase is reported (albeit not a significant one). These data are inconclusive, and it is not certain that the decrease in systemic

absorption observed in the case of the 10 µg regimen does indeed reflect the restoration of the vaginal epithelium (as argued by the opponents), let alone that it correlates with a perceptible symptom relief, which in the present case would appear to be the most relevant criterion for assessing therapeutic efficacy.

4.5 The board therefore considers that the subject-matter of claim 1 of the first auxiliary request is not anticipated by the disclosure of document D13 (Articles 100(a), 52(1) and 54(1)-(2) EPC).

5. First auxiliary request - inventive step

Patent in suit

5.1 It is acknowledged in the patent in suit (see paragraphs [0004] and [0005], citing, *inter alia*, document D2) that Vagifem® 25 µg tablets containing 25 µg estradiol were commercially available for treating atrophic vaginitis, a usual treatment being the topical administration of one tablet daily for two weeks, followed by one tablet twice a week. This corresponds to the dosage regimen specified in the patient information leaflet of Vagifem® 25 µg tablets (see document D9).

5.2 The patent in suit seeks to provide a topical oestrogen treatment of atrophic vaginitis with low systemic absorption, and proposes employing lower doses of estradiol between 9 and 11 µg.

Starting point in the prior art

5.3 The patent proprietor argued that document D2, relating to the long-term treatment of atrophic vaginitis with low-dose (i.e. 25 µg) estradiol vaginal tablets, was the most appropriate starting point for the

assessment of inventive step, and that it was less plausible that the person skilled in the art seeking an efficacious treatment of atrophic vaginitis would have started from the teaching of document D13, which reported on a pharmacokinetic study and did not contain any information on the efficacy of the treatment.

5.4 The board considers that document D13 cannot be ruled out as a possible starting point for the assessment of inventive step, for the following reasons:

5.4.1 Document D13 explicitly mentions that its study subjects were post-menopausal women receiving estradiol in vaginal tablets for the treatment of atrophic vaginitis; see D13, P-16: *"Objective: [...] in postmenopausal women with atrophic vaginitis treated for 12 weeks"* and *"Conclusion: No accumulation of estradiol occurred in postmenopausal women who received either Vagifem (E2, 25 µg) or E2 (10 µg) vaginal tablets for the treatment of atrophic vaginitis"*.

5.4.2 D13 reports that a systemic absorption with 10 µg estradiol tablets and with 25 µg estradiol tablets was compared. The 25 µg estradiol tablets were Vagifem® 25 µg tablets, approved and marketed for the treatment of atrophic vaginitis and therefore generally known to have the desired therapeutic efficacy (see D9 and point 5.1 above, and also D13: abstract P-17 relating to the long-term efficacy of Vagifem® 25 µg tablets).

5.4.3 It would therefore have been evident to the reader of D13 that the tablets tested were destined for the topical treatment of atrophic vaginitis, even if the document focuses in its data on the pharmacokinetic aspect of systemic absorption and does not provide data about the efficacy of the treatment using 10 µg doses.

5.4.4 Moreover, the therapy plan described in document D13 corresponds to the regimen defined in claim 1 of the first auxiliary request (see D13 and point 4.2 above; the tablets were administered once daily for two weeks and then twice weekly for ten weeks).

5.4.5 Since D13 therefore comes very close to the claimed subject-matter both in its object and its technical features (and indeed closer than document D2, which does not suggest employing doses of 9 to 11 µg), it is a workable starting point for the assessment of inventive step.

5.5 If the person skilled in the art had a choice of several workable approaches that might suggest the invention (i.e. several possible starting points), the rationale of the problem-and-solution approach requires that the invention be assessed relative to all these possible approaches before any decision confirming inventive step is taken (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.2). In the present case, a second approach starting from the teaching of document D2 is not necessary, in view of the outcome of the assessment of inventive step starting from D13.

Technical problem and solution

5.6 The disclosure of document D13 differs from the subject-matter of claim 1 solely in not disclosing the efficacy of the 10 µg dosage regimen of estradiol in the topical treatment of atrophic vaginitis.

5.7 On the issue of systemic absorption, document D13 comes to the conclusion that, while the areas under the curve and maximal concentrations of absorbed estradiol were higher in the group receiving the 25 µg tablets, no

accumulation of estradiol by systemic absorption occurred in subjects who received either the 25 µg tablets or the 10 µg tablets. This is consistent with the conclusions presented in the patent in suit (see examples 1 and 2, paragraphs [0034] to [0040]).

5.8 Starting from the teaching of document D13, the technical problem to be solved is thus the provision of a new low-dose form of estradiol for the topical treatment of atrophic vaginitis wherein systemic estradiol exposure is minimised.

5.9 On the basis of the clinical data provided in the patent in suit (obtained with 10 µg doses), the board accepts that the solution to that problem is provided by the subject-matter according to claim 1 of the first auxiliary request, involving the administration of doses from 9 to 11 µg estradiol in a regimen including induction treatment and maintenance treatment.

Obviousness of the solution

5.10 The person skilled in the art seeking to solve the technical problem would routinely test dosages other than the 25 µg known to be efficacious. While different application schemes might be conceivable, obvious tests would be based on the known application scheme (i.e. an induction phase followed by maintenance treatment), employing different doses. In the field of medicine, lowering the dosage is typically desirable with a view to reducing the risk of side effects. More particularly, it was known that systemic absorption might be an issue with topical hormone treatment, as it might pose a risk of unwanted side effects. While it could be inferred from the fact that Vagifem® 25 µg tablets had obtained regulatory approval that there were no great concerns about clinically relevant side

effects with the 25 µg dosage regimen, it was a commonly known general principle that the lowest effective dose should be used in topical hormone therapy to minimise systemic absorption. For these reasons, the person skilled in the art would have considered reducing the dosage of estradiol.

5.11 The patent proprietor contended that the person skilled in the art would not have had a reasonable expectation of success when considering a dosage regimen employing doses lower than 25 µg estradiol, for the following reasons:

5.11.1 The prior art presented a consistent picture, according to which 25 µg was the lowest feasible maintenance dosage. In particular, document D2 clearly taught that 25 µg was considered the lowest effective dose (see D2: page 30, lines 9 to 11 and concluding sentence).

5.11.2 Document D5, relied on by the opponents as a supplementary document on the subject of 10 µg dosing, only disclosed a short-term study. Although it described induction treatment with 10 µg doses, D5 did not contain any information or predictions about the potential efficacy of long-term maintenance treatment.

5.12 Furthermore, according to the patent in suit (paragraph [0024]) maturation of the urethral epithelium was an important component of the treatment of atrophic vaginitis. Document D5 taught that 10 µg doses might not be sufficient to induce maturation of the urethral epithelium (see D5: page 127, Conclusion), which added to the disincentives in the prior art.

5.13 In the board's opinion, it has not been established that there was a prejudice in the art against employing dosages of topical estradiol lower than 25 µg, or that the person skilled in the art would have been

discouraged by strong disincentives from testing the dosage regimen employing 10 µg doses according to D13 because of a lack of reasonable expectation of success.

5.13.1 As a first point, it is not implausible in itself to assume that doses lower than the commercially available 25 µg tablets might still be effective in the treatment of atrophic vaginitis, down to a certain threshold level.

5.13.2 The board considers that no disincentive is given by document D2. The passage cited by the patent proprietor (see D2: page 30, lines 9 to 11) reads as follows:

"This indicates that twice-weekly administration of 25 µg is the lowest effective dose for the long-term treatment of post-menopausal estrogen-deficiency-derived atrophic vaginitis."

While this sentence might seem suggestive when taken in isolation, the general context has to be taken into account. In the clinical study according to D2, patients received induction therapy (daily vaginal administration of 25 µg estradiol) followed by either once-weekly or twice-weekly maintenance treatment. The actual finding of D2 was that twice-weekly administration of 25 µg estradiol was beneficial in bringing about almost complete relief of clinical symptoms (see D2: page 30, lines 4 to 6), while once-weekly administration of 25 µg estradiol was not sufficient to offer complete relief of symptoms, which might be explained by the long interval between the doses (see D2: penultimate paragraph on page 30). The board cannot see how this observation in relation to the frequency of administration would necessarily teach away from the twice-weekly administration of doses lower than 25 µg. Furthermore, document D2 does

not present any experimental data obtained with dosages lower than 25 µg.

5.13.3 As document D13 shows, 10 µg doses had, in fact, already been seriously contemplated by persons skilled in the art. It was also known from D13 that systemic exposure was minimised in the case of 10 µg doses. Hence, D13 provided a strong incentive to verify that 10 µg doses would indeed be therapeutically effective.

5.13.4 Pre-published document D5 provides supplementary information on low-dose estradiol treatment. According to D5, a short-term study was carried out with post-menopausal women with vaginal atrophy, who were treated with vaginal tablets containing either 10 µg or 25 µg estradiol for two weeks (one dose daily) in a double-blind, cross-over study (see D5: summary on page 121; and page 122, paragraph 5). After 14 days of treatment, maturation of the vaginal epithelium was observed for both regimens and the absorption of estradiol then declined significantly on both the 10 µg and the 25 µg dose. Thus, document D5 shows that the induction treatment works equally well with 10 µg doses as with 25 µg doses with regard to the desired maturation of the vaginal epithelium.

5.13.5 According to the patent in suit (see paragraph [0084]), the lower portions of the vaginal and urinary tracts have the same embryological origin, and genital tract disorders such as atrophic vaginitis are often accompanied by atrophic changes in the urinary tract. Consequently, oestrogen therapy may also have an effect on the urethra epithelium. Improved cytological maturation of both the vaginal and urethral mucosa are presented as desirable effects of the topical estradiol treatment (see the patent in suit, paragraph [0024]).

5.13.6 As pointed out by the patent proprietor, while the findings of the study disclosed in document D5 showed no difference in improvement/recovery of the vaginal epithelium as between the 10 and 25 µg regimens (see point 5.13.4 above), the improvements found in the urethral epithelium were significant only in the case of the 25 µg dosage regimen.

However, this cannot be regarded as an absolute disincentive. In fact, document D5 states (see page 126, last sentence), that: "Nevertheless, a certain degree of urethral maturation was seen even at the lower dose, and the fact that all smears were adequate after treatment could also be interpreted as an oestrogenic effect."

In line with that finding, the conclusion presented in D5 (see page 127) is tentative rather than categorical, and certainly does not rule out the further investigation of long-term treatment using 10 µg doses:

"Very low doses of oestradiol might be of value in treating atrophic vaginitis, although the ultra-low dose of 10 µg might not be sufficient to induce maturation of the urethral epithelium, at least during short-term treatment."

In that context, D5 speculates that, since intravaginally administered estradiol cannot act directly on the urethral tissues, a certain elevation of the plasma levels may be necessary to obtain maturation of the urethral epithelium (D5: page 126, lines 9 to 6 from the bottom of the page).

5.13.7 Lastly, the board observes that there is no absolute requirement in claim 1 for urethral efficacy (also keeping in mind that, according to the patent in suit, urethral atrophy does not invariably occur in cases of vaginal atrophy; see point 5.13.5 above), and that

topical vaginal efficacy would thus appear to be the mandatory and therefore more relevant criterion. Nor does claim 1 require the regimen employing doses of 9 to 11 µg to be just as effective as a regimen using 25 µg doses. Depending on the circumstances in the individual case, it might be preferable to ensure that systemic absorption be kept at the lowest possible level.

5.14 In conclusion, the board considers that since, according to the prior art, 10 µg doses were an option which had been seriously contemplated for the low-dose topical treatment of atrophic vaginitis and, moreover, the efficacy of the induction treatment using 10 µg doses was known, the person skilled in the art would not have been discouraged from attempting to verify and confirm the efficacy of a treatment regimen as defined in claim 1, including one with a maintenance treatment with 10 µg doses.

5.15 In order to be able to implement such treatment, the person skilled in the art, taking into account the teaching of D13, merely had to verify that the therapy plan using 10 µg dosages provided the desired therapeutic efficacy. Such verification by carrying out a study to this end did not require inventive skill.

5.16 Consequently, the subject-matter of claim 1 of the first auxiliary request does not involve an inventive step within the meaning of Article 56 EPC.

6. Second and third auxiliary requests

6.1 The dosage of estradiol administered according to document D13 was 10 µg both during pre-treatment (once daily) and maintenance treatment (twice weekly); the duration of the pre-treatment phase was two weeks and

the duration of the maintenance treatment was ten weeks. Hence, claim 1 of the second and third auxiliary requests (defining doses of 10 µg, a duration of the pre-treatment phase of two weeks and, in the third auxiliary request, a duration of the maintenance treatment of more than two months) does not contain any additional technical features distinguishing the claimed subject-matter from the disclosure in document D13 that go beyond those in claim 1 of the first auxiliary request.

6.2 Consequently, the board's assessment with regard to inventive step remains the same as presented above in the context of the first auxiliary request (see section 5). Accordingly, the subject-matter of claim 1 of the second and third auxiliary requests 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.

3. The request for reimbursement of the appeal fee of appellant-opponent 2 is allowed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated