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Datasheet for the decision of 19 October 2021

Case Number: T 1894/17 - 3.3.07

Application Number: 14163637.3

Publication Number: 2786748

IPC: A61K9/70, A61K31/27

Language of the proceedings: EN

Title of invention:
Transdermal therapeutic system comprising rivastigmine

Applicant:
Novartis AG
Novartis Pharma GmbH
LTS LOHMANN Therapie-Systeme AG

Headword:
Rivastigmine TTS / NOVARTIS

Relevant legal provisions:
EPC Art. 123(2), 76(1)

Keyword:
Divisional application - added subject-matter (yes)

Decisions cited:
T 0782/16, G 0002/10

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Case Number: T 1894/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 October 2021

Appellant: (Applicant 1)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Appellant: (Applicant 2)	Novartis Pharma GmbH Brunner Strasse 59 1230 Wien (AT)
Appellant: (Applicant 3)	LTS LOHMANN Therapie-Systeme AG Lohmannstrasse 2 56626 Andernach (DE)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 4 April 2017 refusing European patent application No. 14163637.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	Y. Podbielski
Members:	E. Duval
	M. Steendijk

Summary of Facts and Submissions

I. The appeal was filed by the applicants (appellants) against the decision of the examining division to refuse the European patent application No 14163637.3 (hereinafter "the application"). The application had been filed as a divisional from the earlier application 06816633.9 (hereinafter "the earlier application"), published under the PCT as WO 2007/064407.

II. The decision was based on a main request filed during the oral proceedings on 9 February 2017, auxiliary request 1 filed on 16 November 2015, auxiliary request 2 filed on 25 November 2016, and auxiliary request 3 filed during the oral proceedings on 9 February 2017.

Claim 1 of the main request read as follows:

"Use of rivastigmine for the manufacture of a TTS medicament for use in the prevention, treatment or delay of progression of Alzheimer's disease by transdermal administration, wherein the administration comprises administering a starting dose which is that of a TTS comprising as active ingredient rivastigmine in free base form and having an AUC_{24h} of 45.6 ng•h/mL rivastigmine after repeated once daily administration."

III. The examining division decided as follows.

(a) Claim 1 of the main request extended beyond the content of the earlier application as filed for two reasons.

Firstly, claim 1 of the main request introduced a new teaching, namely that a dosage regimen of rivastigmine characterized by the transdermal administration of the claimed starting dose of the drug was associated with some specific therapeutic effect, deemed to be beneficial in patients with Alzheimer's disease, which could be turned into a practical application in the form of a specified actual treatment of this pathological condition.

Secondly, claim 1 of the main request resulted from an inadmissible generalisation starting from table 2 of the earlier application, namely the isolation of the claimed starting dose from the further features of the four-period titration and of the specific TTS#2.

(b) The same conclusion applied to each of auxiliary requests 1 and 2. As to auxiliary request 3, it did not *prima facie* overcome all the outstanding objections and was not admitted into the proceedings.

IV. With their statement setting out the grounds of appeal, the appellants submitted a main request and auxiliary requests 1-6.

The main request was identical to the main request underlying the decision under appeal.

In claim 1 of auxiliary request 1, the condition to be treated was "mild to moderate Alzheimer's disease", and in claim 1 of auxiliary request 2, "dementia or Alzheimer's disease".

Claim 1 of auxiliary requests 3 and 4 differed from claim 1 of the main request and auxiliary request 1, respectively, in that the starting dose was "that of a TTS which provides an AUC_{24h} of 45.6 ± 16.6 ng•h/mL rivastigmine."

Claim 1 of auxiliary request 5 read as follows:

"Use of rivastigmine for the manufacture of a TTS medicament for use in the prevention, treatment or delay of progression of Alzheimer's disease or dementia associated with Parkinson's disease by transdermal administration, wherein the administration comprises administering a starting dose which is that of a TTS having an AUC_{24h} of about 45 ng•h/mL rivastigmine after repeated once daily administration".

Claim 1 of auxiliary request 6 differed from claim 1 of auxiliary request 5 in that "or dementia associated with Parkinson's disease" was deleted.

V. The Board issued a communication pursuant to Article 15(1) RPBA on 2 July 2021. In this communication, the Board questioned whether the main request and auxiliary requests 1-6 met the requirements of Articles 84 EPC with respect to the expression "starting dose". The Board also set out its preliminary opinion with respect to Articles 76(1) and 123(2) EPC.

VI. By letter dated 20 September 2021, the appellants submitted auxiliary requests 7-13.

Claim 1 of each of auxiliary requests 7-13 corresponded respectively to claim 1 of the main request and auxiliary requests 1-6 wherein the expression "the administration comprises administering a starting dose

which is that of a TTS" was replaced with "the administration starts with administration of a TTS".

VII. With the consent of the appellants, oral proceedings were held on 19 October 2021 by means of a videoconference.

VIII. The arguments of the appellants regarding compliance with Articles 76(1) and 123(2) EPC may be summarized as follows:

According to a first line of argumentation (Derivation A), claim 1 of the main request found basis on page 11 together with example IV of the earlier application. The earlier application related to two aspects, namely a "structural invention" concerning TTS having various pharmaceutical compounds (i.e. not just rivastigmine) and a particular type of adhesive layer, and a "use invention" regarding methods for administering rivastigmine which was not limited to the use of any particular TTS structure. The disclosure on page 11 of the earlier application related to the use invention and made reference to the possibility of a higher starting dose being used. The only *in vivo* example of a starting dose disclosed in the application was that of TTS#2 in example IV which provided an AUC_{24h} of 45.6 ng•h/mL (see table 2). Even though in example IV a specific TTS structure was used to administer rivastigmine, the skilled team knew as part of its common general knowledge that different TTS structures could be manufactured that would provide the same AUC_{24h} as the $5cm^2$ TTS#2, as confirmed on page 9 and in example III of the earlier application.

According to a second line of argumentation (Derivation B), the subject-matter of claim 1 of the main request

was derivable starting from example IV of the earlier application and applying the common general knowledge of the skilled team. Thus, the starting dose specified in the claim could be found in example IV. In this study, a TTS dosage regimen was compared with a known oral dosage regimen for rivastigmine. The TTS dosage regimen started with the 5 cm^2 TTS#2 before being titrated to higher doses, and was shown to be therapeutically effective. According to table 2, this 5 cm^2 TTS#2 provided an AUC_{24h} of 45.6 ng•h/mL as claimed. Although example IV did not use the phrase "starting dose" *verbatim*, explicit support was not necessary: the patient inherently received a starting dose in this TTS dosage regime, just as in any other dosage regime. Furthermore, the generalisation in claim 1 of the main request of this exemplified starting dose, defined by reference to the AUC_{24h} value provided by that starting dose with no specified restriction on the structure of the TTS providing that starting dose, was permissible.

Claim 1 of auxiliary requests 5, 6, 12 and 13 derived from claims 18 and 21-22 of the earlier application as filed, when combined with the disclosure of the earlier application as a whole, in particular page 11, and the skilled team's common general knowledge (Derivation C). The skilled team would have noted from reading the application as a whole, and in particular page 11, that the TTSs of the invention, such as those defined in claim 18, may allow a higher starting dose. The skilled team would have appreciated from the common general knowledge regarding the link between AUC_{24h} and tolerability that the TTS at the lower end of the range claimed in claim 18 would be most suitable for use as the starting dose, i.e. a TTS which has an AUC_{24h} of about 45 ng•h/mL.

IX. The appellants request that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution on the basis of the main request before the examining division at the oral proceedings, or, alternatively, on the basis of one of auxiliary requests 1-6 filed with the grounds of appeal or one of auxiliary requests 7-13 filed on 20 September 2021.

Reasons for the Decision

1. Main request, Articles 76(1) and 123(2) EPC

1.1 The present application was filed as a divisional of the earlier application 06816633.9, itself filed under the PCT and published as WO2007/064407.

In the following, the Board assesses whether the main request meets the criteria of Article 76(1) EPC. Since the application as filed and the earlier application as filed have the same content (the claims of the earlier application as filed being included in the description of the divisional as filed), the same considerations apply correspondingly under Article 123(2) EPC.

The question is whether the subject-matter of claim 1 of the main request remains within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the earlier application as filed as a whole (following the "gold standard" disclosure test, see G 2/10, Reasons 4.3).

1.2 Technical field of the invention

Claim 1 of the main request relates to the use of rivastigmine for the manufacture of a TTS medicament for use in the prevention, treatment or delay of progression of Alzheimer's disease by transdermal administration.

Transdermal therapeutic systems (TTS) are generally known in the art and are devices capable of releasing pharmaceutically active ingredients through the skin, such as transdermal patches (see page 3, penultimate paragraph, of the earlier application). TTSs containing rivastigmine were known in the prior art (see page 1, second paragraph).

Rivastigmine is a known active ingredient used in the treatment of Alzheimer's disease. At the priority date, rivastigmine was approved for use in the treatment of Alzheimer's disease by oral administration. To reduce the adverse events and enable patients to tolerate higher doses, rivastigmine was approved for use in a dose titration regimen which started from a low oral starting dose and then slowly increased to the maintenance dose over a period of time (see the grounds of appeal, point 3).

1.3 Interpretation of claim 1 of the main request

In claim 1 of the main request, the transdermal administration is characterised by a starting dose "which is that of a TTS comprising as active ingredient rivastigmine in free base form and having an AUC_{24h} of 45.6 ng•h/mL rivastigmine after repeated once daily administration". Thus, the subject-matter of claim 1 is not limited to any particular TTS structure or to a

once daily administration. Rather, the subject-matter of claim 1 is only defined by the starting dose corresponding to any TTS having the stated AUC_{24h} after repeated once daily administration.

The expression "starting dose" is not defined in the application. Nonetheless, for the purposes of the present decision, the Board uses the interpretation of "starting dose" proposed by the appellants, namely as the dose of rivastigmine released to the patient, and giving rise to the claimed AUC_{24h} in the patient, at the beginning of a titration dosage regimen. The appellants expressed the view that this dose was correlated with exposure, i.e. with the AUC_{24h}. Considering the Board's conclusion when following the interpretation proposed by the appellants, it is not necessary to assess whether other interpretations are covered by claim 1.

1.4 Disclosure of the earlier application as filed

1.4.1 The earlier application starts by setting out a number of objectives of the invention, relating generally to TTS comprising a broad range of different pharmaceutical compounds, and more particularly to rivastigmine (see page 1, paragraph 4 to page 2, paragraph 2). The third paragraph on page 2 then states that these objectives are achieved by a TTS as defined in claim 1, namely a TTS comprising in particular an adhesive layer comprising a silicone polymer and a tackifier (see also page 3, lines 5-7).

This corresponds to what the appellants call the first aspect or the "structural invention". This disclosure does not as such offer a basis for omitting the structural features of the TTS and defining the

administration by its starting dose as in claim 1 of the main request.

1.4.2 The AUC_{24h} of 45.6 ng•h/mL specified in claim 1 of the main request only appears, in the earlier application as filed, in example IV.

This example IV describes a study carried out on patients with mild to moderate Alzheimer's disease. The patients received either an oral formulation of rivastigmine (Exelon® capsules), or the transdermal formulation TTS#2 described in example I. This TTS#2 is characterised by the structural features of the TTS of the above first aspect (referred to by the appellants as the "structural invention").

The study of example IV comprises four periods with an increasing dosage of the active ingredient. The patients enrolled for the oral therapy received 1.5, 3, 4.5 and 6 mg bid Exelon®. Those enrolled in the transdermal therapy were treated with TTS#2 patches of 5, 10, 15 and 20 cm^2. Tables 1 and 2 report the pharmacokinetic parameters of rivastigmine following capsule administration (Table 1) or the TTS#2 application (Table 2). The pharmacokinetic parameters include the maximum serum concentration (C_{max}), the time at which the C_{max} is observed (t_{max}), the 24-hour area under the concentration-time curve (AUC_{24h}) and the half-life ($t_{1/2}$). The data relate to the four periods.

An average value of 45.6 ng•h/mL for the AUC_{24h} is shown in Table 2 among many other pharmacokinetic parameters, and only for the specific first period of treatment with the TTS#2 of 5 cm^2. Example IV does not identify this specific value as being of any particular

relevance. Furthermore, the study pertains only to the specific patch TTS#2. There is no suggestion in example IV to use another TTS.

1.4.3 The appellants presented the following two lines of reasoning to justify the generalisation of this AUC_{24h} of 45.6 ng•h/mL and the definition of the administration by a corresponding starting dose.

1.5 Derivation A

1.5.1 The appellants, in a first line of argument (Derivation A), consider that claim 1 of the main request finds basis starting from page 11 together with example IV of the earlier application.

Thus, according to the appellants, the earlier application does not only disclose the above first aspect (i.e. the "structural invention", see 1.4.1 above), relating to TTSs having certain structural features and covering a broad range of active ingredients, including rivastigmine. The earlier application would also contain a second, separable "use" or "in use" aspect, pertaining to rivastigmine administration, or to a rivastigmine TTS defined by its properties when used (such as a given AUC_{24h}), without limitation to any TTS structure. To support this view, the appellants refer among others to page 3 (third and fourth full paragraphs), page 9 (first four paragraphs), and independent claims 15-18 of the earlier application as filed. Independent claim 18 in particular relates to a rivastigmine TTS "having an AUC_{24h} of about 45 to 340 ng•h/mL after repeated once daily administration".

The appellants contend that the disclosure on page 11 of the earlier application, which mentions a "starting dose", relates to the use invention. This passage reads as follows:

"The TTS of the invention allows, e.g., the manufacture of once a day pharmaceutical forms for patients who have to take more than one dose of an active agent per day, e.g., at specific times, so that their treatment is simplified. With such compositions tolerability of rivastigmine may be improved, and this may allow a higher starting dose and a reduced number of dose titration steps."

1.5.2 In the Board's opinion, it need not be decided whether the earlier application as a whole discloses this alleged "use invention" independently of the structural features of the TTS of the first aspect. This is because the Board in any case does not see any direct and unambiguous link to this alleged "use invention" in the passage on page 11.

1.5.3 In the first sentence on page 11, the reference to "an active agent" points to the TTS of the first aspect, namely the TTS of claim 1 having a specific structure and any active ingredients, rather than to the TTS of the alleged second aspect, which is limited to rivastigmine. The reference to "such compositions" in the second sentence of page 11 accordingly also points to the same aspect. This is not contradicted by the mention of rivastigmine in the second sentence, since rivastigmine is one of the active agents, and indeed the most preferred one, to be used in the TTS of the first aspect.

Contrary to the appellants' argument, the mention of "patients who have to take more than one dose of an active agent per day" does not imply that the whole passage is limited to rivastigmine, let alone that it pertains to TTSs of the second aspect defined by their AUC_{24h}. The appellants relied on the fact that memantine and donepezil, which are listed among the active ingredients of page 5 of the earlier application as filed, were already approved for once a day use, whereas rivastigmine was not. In the Board's view, there is no evidence that rivastigmine is the sole active ingredient, among those listed in the earlier application as filed, which was not known for once a day use, and thus no reason to read "an active agent" as being limited to rivastigmine.

1.5.4 But even if, for the sake of argument, the passage on page 11 were to be read as being limited to rivastigmine and as encompassing all aspects of the invention, it would still not provide a basis for claim 1 of the main request, for the following reasons.

The second sentence on page 11 relates to rivastigmine compositions possibly ("may") leading to improved tolerability, which in turn "may" allow for a higher starting dose. To the extent that this passage encompasses several embodiments, it does not state which of them will actually allow for a higher starting dose. There is no direct and unambiguous disclosure on page 11 or elsewhere in the earlier application that a rivastigmine TTS solely defined by its AUC_{24h} will lead to this potential higher tolerability and thus will allow this higher starting dose, independently of the TTS structure (as defined in the first aspect) or of e.g. its maximum plasma concentration (as defined in

some embodiments of the alleged second aspect, see page 9, third and fourth paragraph).

Accordingly, the derivation A proposed by the appellants and starting from page 11 is not convincing.

1.6 Derivation B

1.6.1 In a second line of argument (Derivation B), the appellants derive the subject-matter of claim 1 of the main request starting from example IV of the earlier application and applying the common general knowledge of the skilled team.

1.6.2 However, as explained in T 782/16 (point 4.1.3 of the Reasons), the "gold" standard for the assessment of Articles 123(2) and 76(1) EPC requires that the subject-matter of an amended claim (or of a claim of a divisional application) be based only on what the skilled person would directly and unambiguously derive from the application as originally filed (or from the earlier application; see G 2/10, point 4.3 of the Reasons). For a correct application of this standard, a distinction needs to be made between subject-matter which is disclosed either implicitly or explicitly in the original (or earlier) application and therefore can be directly derived from it, and subject-matter which is the result of an intellectual process, in particular a complex one, carried out on what is disclosed.

1.6.3 To arrive at claim 1 of the main request, the reasoning of the applicants comprises the following intellectual steps:

Firstly, the skilled reader would have to single out, from the numerous pharmacokinetic data disclosed in

tables 1 and 2, the AUC_{24h} of the TTS#2 of 5 cm^2 and of the capsules of 1.5 mg in the first step of the titration. The skilled reader would then have to compare these two pieces of data. The appellants contend that this TTS starting dose would leap off the page to the technical audience, because this higher TTS starting dose would permit faster titration and attainment of therapeutic exposure. However, both oral and TTS arms of the study in example IV comprise 4 titration steps. The reasoning based on these anticipated advantages may be a consideration in the context of an inventive step analysis, especially obviousness, but has little to do with direct and unambiguous disclosure.

Secondly, the skilled reader would have to formulate the idea of using any TTS that is capable of providing the same rivastigmine dose as the TTS#2 of 5 cm^2. This supposes not only that the rivastigmine administration be defined solely by its starting dose, or by the AUC_{24h} of the TTS at the start of the dosage regimen, but also that this starting dose be generalised to TTSs of any structure. Contrary to the appellants' view, the absence of an inextricable link between the structure of 5 cm^2 TTS#2 and this particular item of its pharmacokinetic data is not recognisable in the earlier application as filed (see 1.6.4 below).

In sum, the appellants' reasoning is based on an intellectual processing of the subject-matter disclosed in the earlier application, rather than deriving the claimed subject-matter directly and unambiguously from the earlier application as required by Article 76(1) EPC.

1.6.4 The further arguments of the appellants in support of the generalisation from example IV do not modify the Board's conclusion.

In Figures 2 and 3, the permeation of rivastigmine through human skin or EVA membrane is compared for two TTSs differing by the presence (TTS#2) or absence (TTS#1) of the silicone adhesive layer. It is concluded (see the bottom of page 13 to 14, second complete paragraph) that the application of the additional silicone adhesive layer has no influence on active ingredient permeation through the skin. This comparison offers no basis for isolating the starting dose of table 2 from the other features of the TTS#2 and generalising this exposure to any other TTS structure.

Page 9 of the earlier application does not support the view of the appellants that no particular TTS structure is critical for achieving the release characteristics. Rather, page 9 (fifth paragraph) states that the structural features of the TTS (such as the composition, the nature and amount of excipients, the type of the adhesive layer or dimension of the patch) may be chosen so as to achieve the plasma profile mentioned on the same page (see third and fourth paragraphs, "a mean maximum plasma concentration of about 1 to 30 ng/ml from a mean of about 2 to 16 hours after application", or "a mean maximum plasma concentration of about 1 to 30 ng/ml from a mean of about 2 to 16 hours after application and an AUC 24h of about 25 to 450 ng•h/mL after repeated "QD" (i.e. once daily) administration"). Page 9 neither refers to the TTS#2 of 5 cm^2 of example IV or its starting dose, nor offers any basis for generalising the particular AUC_{24h} of 45.6 ng•h/mL shown in table 2 to any TTS structure beyond TTS#2.

1.7 Thus, the subject-matter of claim 1 of the main request cannot be derived from the earlier application as filed using Derivation B either.

1.8 Accordingly, the main request does not meet the requirements of Articles 123(2) and 76(1) EPC.

2. Auxiliary requests 1-4 and 7-11

In claim 1 of each of the auxiliary requests 1-4 and 7-11, as in claim 1 of the main request, the TTS is structurally undefined and the administration starts with a TTS, or a starting dose corresponding to a TTS, providing the AUC_{24h} of 45.6 ng•h/mL.

Accordingly, auxiliary requests 1-4 and 7-11 do not comply with the requirements of Articles 76(1) and 123(2) EPC for the same reasons as the main request.

3. Auxiliary requests 5, 6, 12 and 13

3.1 In claim 1 of each of auxiliary requests 5, 6, 12 and 13, the administration starts with a dose or a TTS defined by reference to an AUC_{24h} of "about 45 ng•h/mL".

With respect to these auxiliary requests, the appellants rely on a further derivation (Derivation C) starting from claims 18 and 21-22 of the earlier application as filed. Claim 18 mentions a rivastigmine TTS having an AUC_{24h} of about 45 to 340 ng•h/mL after repeated once daily administration.

However, none of claims 18 and 21-22 of the earlier application as filed define the TTS treatment by a

starting dose corresponding to a TTS having this AUC_{24h}, or by the TTS used at the start of the administration. The appellants contend that it would be natural to take the lower end of the range in claim 18 for the starting dose. In the Board's opinion, this argument may at most make the choice of this value obvious, but it falls short of a direct and unambiguous disclosure of an administration starting with this value.

Furthermore, for the reasons given above, neither page 11 nor example IV provide a disclosure of an administration defined solely by its starting dose or TTS.

Consequently, auxiliary requests 5, 6, 12 and 13 do not comply either with the requirements of Articles 76(1) and 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

B. Atienza Vivancos Y. Podbielski

Decision electronically authenticated