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Datasheet for the decision of 26 September 2019

Case Number: T 1732/16 - 3.3.02

Application Number: 07788151.4

Publication Number: 2046745

IPC: C07D211/90

Language of the proceedings: EN

Title of invention:
PROCESS FOR PREPARING AMORPHOUS LERCANIDIPINE HYDROCHLORIDE

Patent Proprietor:
Recordati Ireland Limited

Opponent:
Actavis Group PTC ehf

Headword:

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:
Inventive step
Late-filed facts
Late-filed auxiliary requests

Decisions cited:

Catchword:

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Case Number: T 1732/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 26 September 2019

Appellant: (Patent Proprietor)	Recordati Ireland Limited Raheens East Ringaskiddy County Cork (IE)
Representative:	Pistolesi, Roberto Dragotti & Associati Srl Via Nino Bixio, 7 20129 Milano (IT)
Respondent: (Opponent)	Actavis Group PTC ehf Reykjavikurvegi 76-78 220 Hafnarfjördur (IS)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 2 May 2016 revoking European patent No. 2046745 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	P. de Heij

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the proprietor (appellant) against the decision of the opposition division to revoke European patent no. 2 046 745 (patent in suit).

II. In its notice of opposition, the opponent (respondent) requested the revocation of the patent in its entirety based on, *inter alia*, Article 100(a) EPC (lack of inventive step). The documents submitted during the opposition proceedings included:

D1 US 4,705,797
D6 US 5,912,351
D8 WO 2006/037650 A1

III. On 7 December 2018, at the respondent's request, the original date for the oral proceedings was postponed to 26 September 2019.

IV. With its letter dated 3 June 2019, the appellant filed sets of claims of a new main request and a new first to third auxiliary request. These requests were intended to replace those filed with its statement of grounds of appeal. With the same letter, the appellant also filed:

D9 experimental evidence entitled "Preparation of Amorphous Lercanidipine Hydrochloride"

V. With its letter dated 25 July 2019, the appellant filed a revised version of D9, D9', in which it had corrected errors contained in D9.

VI. Oral proceedings before the board were held on 26 September 2019.

VII. The appellant requests that the decision under appeal be set aside and that the patent be maintained on the basis of the sets of claims of:

- the main request or, alternatively
- the first to third auxiliary requests, all filed with its letter dated 3 June 2019

VIII. The respondent requests that the appeal be dismissed.

IX. The appellant's submissions, in as much as they are relevant to the present decision, can be summarised as follows.

The process of the main request and the first and second auxiliary requests differed from D8 in that water was already present when water, intended to precipitate the product amorphous lercanidipine hydrochloride, was added. The skilled person would have understood the feature "*lercanidipine*" in step (a) of claim 1 of the main request to refer to lercanidipine free base. As was clear from examples 1A and 1B in the patent in suit and the examples in D9/D9', the process always resulted in amorphous lercanidipine hydrochloride in high purity and high yield. The objective technical problem was the provision of a process for the manufacture of amorphous lercanidipine hydrochloride in high purity and high yield. D8 did not indicate which solvents were to be used in its process. The formation of a viscous solution in step (b) was only observed with the solvents mentioned in step (a) of the claimed process. According to D8 (paragraph [6]), lercanidipine and its salts were virtually insoluble in water. Thus, the skilled person would not have expected the formation of a viscous solution but

the formation of a precipitate in step (b) of the claimed process. However, examples 1A and 1B in the patent in suit and the examples in D9/D9' showed additional quantities of water to be necessary for precipitation to occur. The process of D8 started from lercanidipine hydrochloride. Saying that the first and second auxiliary requests were obvious because an *in situ* modification starting from lercanidipine free base would have been obvious to the skilled person, was based on hindsight.

The process of the first auxiliary request was simpler than that disclosed in D8 as it did not require the preparation and isolation of lercanidipine hydrochloride beforehand. It was also cheaper because lercanidipine hydrochloride was more expensive than lercanidipine free base. The objective technical problem was the provision of a simpler process for the manufacture of amorphous lercanidipine hydrochloride in high purity and high yield.

The choice of EtOH and/or acetone as the solvent in step (a) of the second auxiliary request resulted in higher yields.

The third auxiliary request was based on the second auxiliary request. It was consistent with the arguments presented in the first-instance proceedings and also clearly allowable. It should be admitted.

X. The respondent's submissions, in as much as they are relevant to the present decision, can be summarised as follows.

The process disclosed in paragraph [25] of D8 was the closest prior art. The features distinguishing the

subject-matter of the main request and the first and second auxiliary requests from D8 were not linked to a technical effect. It was not credible that a high yield and a high purity where achieved over the whole breadth of the claimed process. The objective technical problem was the provision of an alternative process for the manufacture of amorphous lercanidipine hydrochloride. Starting from D8, the skilled person would have arrived in an obvious manner to the subject-matter of the main request and the first and second auxiliary requests. Both ethanol and acetone were common solvents and choosing one of them did not require inventive effort. It also followed from D1 and D6 that they were suitable for dissolving lercanidipine free base and lercanidipine hydrochloride. According to the patent in suit, one embodiment of the main request started from lercanidipine hydrochloride. Contacting a solution containing it with a water HCl solution was non-sensical and did not offer any advantage. When starting from D8, it would have been obvious to the skilled person that the starting material lercanidipine hydrochloride could also be prepared *in situ* from lercanidipine free base instead. Both the process of D8 and the patent in suit employed water to precipitate amorphous lercanidipine hydrochloride - albeit in a different order of addition. Reversing the order of addition would have been an obvious measure for the skilled person.

The appellant's reformulation of the objective technical problem in respect of the first auxiliary request was presented for the first time during the oral proceedings. Similarly, the allegation of fact that the choice of EtOH and/or acetone as the solvent in step (a) of the process of the second auxiliary request was important for the yield was presented for

the first time during the oral proceedings. Both should not be admitted.

The third auxiliary request was filed late. Upon filing, it was hardly substantiated. Arguments as to inventive step were only presented during the oral proceedings. These raised complex new issues which the respondent could not be expected to deal with without adjournment of the oral proceedings. The third auxiliary request should not be admitted.

Reasons for the Decision

Admittance of the main request, the first and second auxiliary requests, and D9 and D9'

1. The main request, the first and second auxiliary requests, and experimental evidence D9 and D9' were filed by the appellant after oral proceedings had been arranged. During the oral proceedings, the board decided to admit these requests and pieces of evidence into the proceedings. As set out below, these requests are not allowable even when taking D9 and D9' into account. In view of this, reasons for the admittance of the requests and pieces of evidence do not need to be given.

Main request - Inventive step (Article 56 EPC)

2. Claim 1 of the main request reads as follows:

"*A process for the manufacture of amorphous lercanidipine hydrochloride which comprises*

(a) dissolving lercanidipine in an oxygenated organic solvent selected from (C_1-C_6) alkanols and/or (C_3-C_6) ketones to form a first solution,
(b) contacting such a first solution with a second water HCl solution,
(c) adding water and,
(d) recovering the precipitated amorphous lercanidipine hydrochloride."

3. In its communication pursuant to Article 15(1) RPBA, the board had indicated that it considered D8, and specifically the process for the manufacture of amorphous lercanidipine hydrochloride disclosed in paragraph [25], as the closest prior art. This was not contested by the appellant, neither with respect to the main request nor the auxiliary requests.

D8 (paragraph [25]) discloses that:

"*[a]morphous lercanidipine hydrochloride may be prepared by*

*(A) **dissolving** crystalline **lercanidipine hydrochloride in an organic solvent** at a first temperature in the range from about 30°C to about 50°C **to form a first solution,***
*(B) **adding the first solution to water** at a temperature in the range from about 1°C to about 20°C **to form a precipitate,** maintaining the precipitate at a temperature in the range from about 1°C to about 20°C, for a period from about 4 to about 24 hours, and*
*(C) **recovering the amorphous lercanidipine hydrochloride.***"

The numbering (A) to (C) is added by the board to make it easier to refer to the different steps of this process; the relevant text passages with regard to claim 1 are emphasised in bold.

4. Distinguishing features

4.1 Claim 1 - step (a)

The process of claim 1 of the main requests starts with "*dissolving* ***lercanidipine*** *in an oxygenated organic solvent*". By contrast, the process of D8 starts with "*dissolving crystalline* ***lercanidipine hydrochloride*** *in an organic solvent*" (emphases added).

In line with the appellant's argument and in its favour, it is assumed below that "*lercanidipine*" in step (a) of claim 1 refers to lercanidipine free base. The starting material used in claim 1 ("*lercanidipine*") thus differs from that of D8 ("*lercanidipine hydrochloride*").

Furthermore, the process of claim 1 is more specific in that it requires the organic solvent to be "*selected from (C_1-C_6) alkanols and/or (C_3-C_6) ketones*".

4.2 Claim 1 - steps (b) and (c)

As is evident from paragraph [0021] in the patent in suit, step (c) in claim 1 serves to precipitate the final product, i.e. amorphous lercanidipine hydrochloride. The same holds true for step (B) of the process of D8 as is immediately clear from its wording. Since both steps essentially serve the same purpose, they correspond to one another. Yet they still differ from each other as regards the order of addition. In

claim 1, water is added to the solution of lercanidipine; in D8, it is the other way around.

Furthermore, there is no step in the process of D8 which would correspond to step (b) in claim 1.

4.3 Claim 1 - step (d)

Step (d) in claim 1 corresponds to step (C) of the process of D8.

4.4 In summary, the process of claim 1 is distinguished from the process of D8 in that:

(i) the starting material is different, namely, lercanidipine free base compared to lercanidipine hydrochloride in D8
(ii) the organic solvent in step (a) is "*selected from (C_1-C_6) alkanols and/or (C_3-C_6)ketones*"
(iii) it comprises an additional step (b) wherein the first solution obtained in step (a) is contacted with a water HCl solution
(iv) the order of addition in step (c) is reversed

Instead of regarding additional step (b) of claim 1 as a distinguishing feature vis-à-vis D8, the solution of lercanidipine could also be seen to already contain water (and HCl) when additional water is added. However, both ways of formulating this distinguishing feature are synonymous, and its actual formulation has no impact on the subsequent assessment.

5. As regards the problem to be solved by these distinguishing features, the appellant pointed to

examples 1A and 1B in the patent in suit as well as the examples provided in D9/D9'. It argued that high purities and high yields were obtained. This was indicative of an inventive step.

This argument cannot be accepted. For the examples of the patent, the purities of the starting materials is not given. Furthermore, as indicated by the appellant in its letter dated 25 July 2019, in the 19 examples of D9/D9', the starting materials already had high purities, namely, 99.85% (lercanidipine free base) and 99.88% (lercanidipine hydrochloride). There is thus no proof at all that a high yield and a high purity can be obtained when starting from materials having low purity as covered by claim 1. The problem referred to by the appellant is thus not credibly solved over the entire scope of claim 1.

In this context, the appellant pointed to paragraph [0021] of the patent in suit and argued that it was the choice of the two solvents in step (a) of claim 1 which led to the formation of a viscous solution after step (b).

This argument is not persuasive. The interim occurrence of a viscous solution during the process has not been shown to be linked to a technical effect, let alone a high yield or a high purity.

6. It follows that the objective technical problem is merely the provision of an alternative process for the manufacture of amorphous lercanidipine hydrochloride.

7. Obviousness

7.1 D8 does not indicate any specific solvent to be used in the process described in paragraph [25] (distinguishing feature (ii) above). Thus, when seeking to implement the process of D8, the skilled person would have been confronted with the question of which organic solvent to choose. In doing so, they would have started with the most ubiquitous organic solvents available such as ethanol (a C_2-alkanol) or acetone (a C_3-ketone), i.e. solvents falling within the definition "*$(C_1$-$C_6)$ alkanols and/or $(C_3$-$C_6)$ketones*" in claim 1. In addition, D1 (example 16) teaches that lercanidipine is soluble in methanol (a C_1-alkanol) and that lercanidipine hydrochloride is soluble in acetone. In a similar manner, D6 (example 1) teaches that acetone helps to dissolve lercanidipine in diethyl ether.

7.2 As explained above, the process of D8 starts from lercanidipine hydrochloride, dissolves it in an organic solvent and goes on to add this solution to water to precipitate amorphous lercanidipine hydrochloride (distinguishing features (i) and (iii) above).

It was common ground between the parties that distinguishing features (i) and (iii) above lead to the formation of lercanidipine hydrochloride *in situ* during step (b).

Being confronted with the process of D8, the skilled person would have realised that it was of no relevance for the final product how the solution of lercanidipine hydrochloride was prepared. This is because the lercanidipine hydrochloride "does not know where it came from" as stated by the respondent during the oral proceedings. Given that the way this solution was or is

prepared is irrelevant, it would also have been obvious that it could be prepared *in situ* in the course of the actual process. The respondent held, and this was not contested by the appellant, that the most straightforward way to prepare lercanidipine hydrochloride was to react lercanidipine free base and HCl. Given this, it would have been obvious to the skilled person to modify the process disclosed in paragraph [25] of D8 in such a way that lercanidipine free base is first dissolved and then transformed *in situ* into its hydrochloride by bringing it into contact with, for example, a water HCl solution.

7.3 Lastly, without any indication to the contrary, the reversal of the order of addition (distinguishing feature (iv) above) would have been a routine measure for the skilled person and would not have required any inventive skills.

7.4 In summary, when starting from the process disclosed in paragraph [25] of D8, the skilled person would only have had to apply obvious measures to arrive at the subject-matter of claim 1, making it one of, possibly several obvious alternatives. Therefore, claim 1 does not involve an inventive step and the main request is not allowable.

First auxiliary request - Inventive step (Article 56 EPC)

8. Claim 1 of the first auxiliary request differs from claim 1 of the main request only in that the starting material in step (a) is "*lercanidipine* ***free base***" (emphasis added).

Based on the assessment of the subject-matter of claim 1 of the main request, the process of claim 1 of the

first auxiliary request is distinguished from the process of D8 in that:

(i) the starting material in step (a) is "*lercanidipine free base*"
(ii) the organic solvent in step (a) is "*selected from (C_1-C_6) alkanols and/or (C_3-C_6)ketones*"
(iii) it comprises an additional step (b) wherein the first solution obtained in step (a) is contacted with a water HCl solution
(iv) the order of addition in step (c) is reversed

9. Consequently, the distinguishing features are the same as for the main request. Hence, for the same reasons as given for the main request, the first auxiliary request lacks inventive step.

10. For the first time during the oral proceedings, the appellant argued that the process of claim 1 was simpler than the process of D8. Both lercanidipine hydrochloride and lercanidipine free base were commercially available. Since the former, however, was always prepared from the latter, the hydrochloride had to be more expensive than the free base. The process of D8 started from lercanidipine hydrochloride which meant that it had to be prepared from the free base and isolated beforehand. This required two additional steps (i.e. preparation and isolation) which had to be factored in when counting the actual number of steps of the process disclosed in paragraph [25] of D8. Overall, the process of D8 required more steps than that of claim 1. According to the appellant, the objective technical problem was the provision of a simpler

process for the manufacture of amorphous lercanidipine hydrochloride in high purity and high yield.

The process of claim 1 starts from lercanidipine free base and requires the four steps (a) to (d). The process disclosed in paragraph [0025] of D8 starts from lercanidipine hydrochloride and requires the three steps (A) to (C). Since the starting materials of both processes are commercially available (as conceded by the appellant, see above), it is not self-evident to the board that the process according to claim 1 is necessarily simpler than that of D8. The mere allegation that lercanidipine hydrochloride is always prepared from lercanidipine free base and thus has to be more expensive is not convincing in the absence of tangible evidence. Quite to the contrary, D8 (paragraph [26]) describes the preparation of lercanidipine free base by alkalisation of lercanidipine hydrochloride. To accept the proposed improvement would anyway require to establish how both compounds are produced, what technical steps are required and whether, together with the steps of the claimed subject-matter, overall the claimed process requires fewer process steps to acquire the amorphous lercanidipine hydrochloride. The fact that the appellant raised these complex issues for the first time during the oral proceedings made it impossible for the board and the respondent to deal with them without adjournment of the oral proceedings. Thus, the board decided not to admit the appellant's new formulation of the objective technical problem ("the provision of a simpler process for the manufacture of amorphous lercanidipine hydrochloride in high purity and in high yield") into the proceedings pursuant to Article 13(1) and 13(3) RPBA.

Second auxiliary request - Inventive step (Article 56 EPC)

11. Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request only in that the oxygenated organic solvent in step (a) is "*selected from EtOH and/or acetone*".

Based on the assessment of the subject-matter of claim 1 of the main and the first auxiliary requests, the process of claim 1 of the second auxiliary request is distinguished from the process of D8 in that:

(i) the starting material in step (a) is "*lercanidipine free base*"
(ii) the organic solvent in step (a) is "*selected from EtOH and/or acetone*"
(iii) it comprises an additional step (b) wherein the first solution obtained in step (a) is contacted with a water HCl solution
(iv) the order of addition in step (c) is reversed

12. Again for the first time during the oral proceedings, the appellant argued that the choice of the solvents in step (a) in claim 1 (i.e. distinguishing feature (ii) above under point 11) was linked to a higher yield. This was evident from the experimental data in D9/D9', e.g. from a comparison of examples 2/3 with examples 5/6 using the solvents acetone and ethyl methyl ketone, respectively.

D9/D9' describe 19 experiments. The final products are characterised as to whether they are amorphous and with respect to their purity. The yields obtained are also reported. In the letter accompanying D9, the relevance of the experimental data is only discussed with regard

to purity in general, no connection is made as to the importance of the choice of specific solvents, let alone the choice of solvents as regards yields (the letter accompanying D9' merely addresses the corrections vis-à-vis D9 without discussing the merits of the experimental data). The appellant's submission that the choice of the solvents in step (a) in claim 1 was linked to a higher yield is therefore a new allegation of fact submitted for the first time during oral proceedings. The appellant's argument that these data were reported in D9/D9', that the relation between solvents and yield was immediately apparent and as a consequence that this new allegation of fact should be admitted is not convincing. Submitting experimental data but demonstrating their significance or drawing conclusions from them only during the oral proceedings is generally not acceptable in contentious proceedings as it would deprive the other party of the opportunity to react appropriately by, for instance, filing counter-evidence. In light of this, the board decided not to admit the appellant's new allegation of fact that the choice of the solvents in step (a) in claim 1 is linked to a higher yield pursuant to Article 13(3) RPBA.

13. Apart from the submissions laid out under the preceding point, the appellant relied on its submissions as to the higher ranking requests.

The reasoning above applying *mutatis mutandis*, the distinguishing features identified above are not linked to a technical effect. The objective technical problem is therefore the provision of an alternative process for the manufacture of amorphous lercanidipine hydrochloride.

14. As is clear from the above, the choice of "*(C_1-C_6) alkanols and/or (C_3-C_6)ketones*" for the oxygenated organic solvent in step (a) of claim 1 in the main request and also the choice of the more specific solvents "*EtOH and/or acetone*" would have been obvious to the skilled person.

It follows that the subject-matter of claim 1 does not involve an inventive step and that the second auxiliary request is not allowable.

Third auxiliary request - Admittance (Articles 13(1) and 13(3) RPBA)

15. Claim 1 of the third auxiliary request differs from claim 1 of the second auxiliary request only in that the amount of water added in step (c) is specified as "*from 10 to 100 volumes*".

16. During the oral proceedings, the respondent requested that the third auxiliary request not be admitted into the proceedings.

17. The appellant argued that claim 1 was merely the result of a combination of claims 1 and 4 of the second auxiliary request. This could not have taken the respondent by surprise. Moreover, this development was fully consistent with the appellant's arguments before the opposition division. The claimed subject-matter was also clearly allowable as the prior art taught in a completely different direction. Reading step (c) of claim 1 in light of paragraph [0019] of the patent in suit, it would have been clear that it required much less water for precipitation than did, for instance, D1 (example 16) for recrystallisation. The much lower

upper limit "*to 100 volumes*" in claim 1 was therefore indicative of an inventive step.

The third auxiliary request was filed after the appellant had filed its statement of grounds of appeal. It was not filed in reaction to new developments in the proceedings caused by the board or the respondent. It was therefore filed late. Also upon filing, the appellant merely pointed to its basis in the application as filed and explained why it was convergent with respect to higher ranking requests. Other requirements, i.e. inventive step and the alleged clear allowability resulting from it, were discussed during the oral proceedings for the first time. Whether this request is fully consistent with the appellant's submissions during the opposition proceedings is irrelevant in view of Article 12(2) RPBA stating that the statement of the grounds of appeal shall contain a party's complete case. By addressing inventive step for the first time only during oral proceedings, the appellant raised complex new issues, including the criticality of the upper limit in claim 1 and the allegation that the prior art teaches away from it. The respondent could not reasonably be expected to deal with these issues without adjournment of the oral proceedings. For these reasons, the board decided not to admit the third auxiliary request into the proceedings pursuant to Article 13(1) and 13(3) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated