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**Datasheet for the decision
of 8 November 2013**

Case Number: T 0457/09 - 3.3.07

Application Number: 03016945.2

Publication Number: 1500390

IPC: A61K9/20, A61K38/11

Language of the proceedings: EN

Title of invention:

Pharmaceutical desmopressin composition as solid dosage form
and method for manufacturing thereof

Patent Proprietor:

Ferring B.V.

Opponents:

PH&T S.p.A.
Pliva Pharma Limited
Gebro Pharma GmbH
Alpex Pharma S.A.

Relevant legal provisions:

EPC Art. 56
RPBA Art. 13

Keyword:

Inventive step - improvement not credible
Late-filed auxiliary requests - amendments after arrangement
of oral proceedings - justification for late filing (no)



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Chambres de recours**

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Case Number: T 0457/09 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 November 2013

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
29 December 2008 concerning maintenance of the
European Patent No. 1500390 in amended form.**

Composition of the Board:

Chairman: J. Riolo
Members: D. Semino
P. Schmitz

Summary of Facts and Submissions

- I. The appeals of opponents 01, 02 and 03 (appellants) lie against the decision of the opposition division announced at the oral proceedings on 6 November 2008 to maintain European Patent 1 500 390 as amended.
- II. Four notices of opposition were filed against the granted patent requesting revocation of the patent in its entirety on the grounds of lack of novelty, lack of inventive step and insufficiency of disclosure in accordance with Article 100(a) and (b) EPC. At a later stage opponent 02 invoked the grounds under Article 100(c) EPC by submitting that the subject-matter of the patent extended beyond the content of the application as filed.
- III. During opposition proceedings the following documents were *inter alia* cited:
- E1: WO-A-97/15297
E3: "L'Informatore Farmaceutico", OEMF spa, 2001, pages 715 and 716
E3A: Translation into English of E3 (section concerning "Minirin[®]/DDAVP Compresse")
E27: Minirin tablets 0.1 mg and 0.2 mg, Complete composition of commercial product
E29: US-A-6 024 981
E29a: US-A-5 234 957
E33: US-A-2003/0091637
E34: EP-A-0 517 211
- IV. The decision was based on a single set of amended claims filed with letter of 27 March 2007 as main request and on an amended description filed during oral proceedings on 6 November 2008.

Claim 1 according to the main request read as follows:

"1. A pharmaceutical composition as a solid dosage form comprising desmopressin, or a pharmaceutically acceptable salt thereof, as a therapeutically active ingredient together with a pharmaceutically acceptable excipient, diluent or carrier, or mixture thereof, wherein the pharmaceutical composition is composed of a compressed granulate and contains lubricant in an amount of from 0.05 to 0.40 percent by weight of said pharmaceutical composition, and wherein starch is present as a pharmaceutically acceptable excipient, diluent or carrier."

V. The decision of the opposition division can be summarised as follows:

Amendments, Sufficiency, Novelty

- a) The arguments on extension of the subject-matter beyond the content of the application as filed were *prima facie* not convincing and the ground for opposition under Article 100(c) EPC was inadmissible as late filed. The invention in the patent was sufficiently disclosed as there was a working example, the skilled person was aware of various well-known process parameters which could be adjusted and no convincing evidence of lack of sufficiency was provided by the opponents (Article 100(b) EPC). The composition of claim 1 was novel over documents E1, E29, E29a and E33, as multiple selections within the disclosures of these documents were needed in order to arrive at the claimed subject-matter and over document E34, as example 1 therein could not be combined with the

general teaching of the document in view of a contradiction between the content of magnesium stearate in example 1 and the general disclosure in the document.

Inventive step

- b) The composition of claim 1 was inventive over E3 or E27, taken as closest prior art. The compositions of E3 and E27 differed from the claimed one in the amount of lubricant, which was reduced and lay in the range 0.05 to 0.40%. The problem was the control of the desired hardness in balance with the highest possible compressing speed, reduced machine wear, reduced tablet rupture and satisfactory pharmaceutical properties. As to the credibility of the proposed solution, the burden of proof was with the opponents, who did not provide convincing evidence that the problem was not solved. While it would have been obvious to decrease the amount of lubricant, if the problem had resided only in the increase of tablet hardness, it was not obvious in view of the available prior art to reduce the lubricant amount in order to solve the multi-folded problem, as it was not expected that by reducing the amount of lubricant the compressing speed, the machine wear, the tablet waste and the pharmaceutical properties were improved.

VI. The appellants lodged an appeal against that decision. With their statements setting out the grounds of appeal, all appellants contested *inter alia* the decision on inventive step on the basis that the evidence on file did not support that the problem as

formulated in the appealed decision had effectively been solved.

- VII. With the reply to the statements setting out the grounds of appeal sent with letter of 23 November 2009 the patent proprietor (respondent) submitted three sets of claims as auxiliary requests I to III.

Claim 1 of auxiliary request I corresponded to claim 1 of the main request with the further specification that "the solid dosage form is a perorally available tablet". Claim 1 of auxiliary request II contained in addition the feature that the solid dosage form "comprises desmopressin acetate in an amount of from 20 to 600 µg per tablet". In claim 1 of auxiliary request III the word "lubricant" was additionally replaced by "magnesium stearate".

- VIII. In a communication sent in preparation of oral proceedings the Board *inter alia* with regard to inventive step expressed "doubts that the data available in the patent provide sufficient evidence for the multi-folded problem" (paragraph 5.3) and pointed to the possible consequences for the assessment of inventive step.

- IX. Oral proceedings were held on 8 November 2013. During the oral proceedings the respondent filed a further set of claims as auxiliary request IV. Claim 1 of auxiliary request IV corresponded to claim of the Main Request with the addition that "the granulate has an average size of at least 100 µm, preferably in the range of from 100 µm to 2 µm, more preferably in the range of from 100 to 600 µm, and a size distribution where at least 50%, preferably from 50 to 90%, by volume thereof consists of granulate particles with a size of at least

100 μm , preferably in the range of from 100 μm to 2 μm , more preferably in the range of from 100 to 600 μm ".

X. The arguments of the appellants, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step

- a) The composition of claim 1 differed from the product of E3 and E27 in the amount of lubricant, which was reduced from 0.50% to between 0.05 and 0.40% by weight. The tests available on file were unreliable and inconclusive, as no direct comparison with the product of the closest prior art was made and there were several parameters which were changed at the same time, including in particular the granulate particle size distribution, which had a strong influence on all the properties. While it could be accepted that the reduction in the amount of lubricant could cause an increase in hardness, an improvement in the compression speed was not reasonably shown and there were no comparative data at all for machine wear, tablet waste and pharmaceutical properties. Compression speed in particular was surely affected by the granulate particle size distribution as attested also by the example of E18, which showed in addition that the same result as in the patent could be obtained with a lubricant amount of 0.50%. As the burden of proof related to the achievement of advantages and improvements with respect to the closest prior art lay with the patent proprietor, it could not be accepted that a multi-folded problem had been solved. The problem was therefore the provision of tablets for oral administration with increased

hardness with respect to the ones of E3 and E27. It was an obvious measure for the skilled person to reduce the amount of lubricant in order to increase the tablet hardness, as acknowledged by the opposition division and even by the respondent. This conclusion was supported by a large number of documents in the proceedings and led to the lack of inventive step of the composition of claim 1 of the main request.

Auxiliary requests I to III

- b) The same arguments on lack of inventive step as developed for claim 1 of the main request were equally applicable to claim 1 of auxiliary requests I to III, as there were no additional distinguishing features.

Auxiliary request IV - admissibility

- c) The very late filing of auxiliary request IV at the oral proceedings before the Board was not justified. The issues possibly relevant for that request, including the differences in particle size distribution in the examples in the patent and the concerns arising from the example of E18, had been on file for a very long time. In spite of that, the respondent had decided not to file further requests in first instance proceedings, nor at the time of filing the reply to the statements of grounds.

XI. The arguments of the respondent, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step

- a) The composition of claim 1 differed from the product of E3 and E27 in the amount of lubricant, which was reduced from 0.50% to between 0.05 and 0.40% by weight. There were several effects achieved by the reduction in the amount of lubricant. By means of that measure, the hardness of the tablets could be controlled, while at the same time increasing the production speed, reducing machine wear and tablet rupture and optimising the pharmaceutical properties. The examples in the patent showed the possibility of producing harder tablets with high production speed and adequate quality and confirmed the achievement of those effects. Those examples could not be invalidated by the example of E18, which was not prior art and showed an alternative way of achieving the desired effects, namely by selecting the appropriate particle size distribution of the granulate. While it was true that some properties could be influenced by the particle size distribution, it was the effect of the lubricant which was analysed in the patent in suit. The achievement of the desired effects was not invalidated by any counter-evidence of the appellants, which decided not to produce any, even after the invitation of the opposition division. In this respect, the case law set the burden of proof on the opponent to show that the effects had not been achieved and the posed problem had not been solved, as confirmed by a large number of decisions. The problem solved by the claimed invention was therefore that of obtaining and controlling the desired hardness in balance with the highest possible compression speed, reduced

machine wear, reduced tablet rupture and adequate pharmaceutical properties. The five aspects of the problem were interdependent and it was not obvious that the right balance could be found by decreasing the amount of lubricant. On the contrary, the effect of the lubricant on some properties was counter-intuitive. While it was known that a decrease in the lubricant amount could cause an increase in hardness, none of the documents on file suggested to go below the amount of 0.50%.

Auxiliary requests I to III - inventive step

- b) The composition of claim 1 of auxiliary requests I to III were inventive for the same reasons as outlined for the main request.

Auxiliary request IV - admissibility

- c) The filing of auxiliary request IV at the oral proceedings before the Board was justified by the questions raised by the Board with regard to the presence of the claimed technical effects. The experimental data in the patent were even more relevant with two distinguishing features, namely the lubricant amount and the particle size distribution of the granulate, with respect to the closest prior art. The introduction of those features into claim 1 could not be a surprise for the appellants in view of the objections they had raised in appeal and it had even be suggested by them.

XII. The appellants requested that the decision under appeal be set aside and that the patent be revoked. They

additionally requested that auxiliary request IV be not admitted into the procedure because it was late filed.

- XIII. The respondent requested that the appeals be dismissed, alternatively that the decision under appeal be set aside and that the patent be maintained on the basis of any of auxiliary requests I to III filed with letter of 23 November 2009, or auxiliary request IV filed during the oral proceedings before the Board.

Reasons for the Decision

Main request - inventive step

1. There was agreement among the parties in the choice of the commercial product Minirin[®], as disclosed in documents E3 (see in particular the translation into English of the relevant section E3A) and E27 and also mentioned in the patent (paragraph [0006]), as the closest prior art and in the identification of the difference between the composition of claim 1 of the main request and the product Minirin[®].
- 1.1 Minirin[®] is a compressed granulate in the form of a tablet containing desmopressin acetate, lactose monohydrate, magnesium stearate (a lubricant, see granted claim 7) at 0.50% by weight, povidone and potato starch (see E3A and E27 and paragraph [0006] in the patent), so that the composition of claim 1 differs from the known product only in the amount of lubricant, which is 0.05 to 0.40% by weight in the claimed composition and 0.50% by weight in the product Minirin[®].
2. The main point of dispute among the parties related instead to the identification of the effects and advantages of the claimed product with respect to the

- known one in view of the acknowledged difference and the consequent formulation of the solved problem.
- 2.1 The respondent in agreement with the decision under appeal (paragraph 22 of the reasons) and with the patent in suit (paragraphs [0005] and [0006]) posed the problem as how to obtain and control the desired hardness in balance with the highest possible compressing speed, reduced machine wear, reduced tablet rupture and desirable pharmaceutical properties. According to the appellants the problem was only the increase in the hardness of the solid dosage form.
- 2.2 The evidence available on file has therefore to be analysed in order to determine which effects and advantages have been credibly shown and which problem has effectively been solved.
- 2.3 The tests in example 1 of the patent (paragraphs [0050] to [0053]) compare a tablet according to the invention and containing 0.25% by weight of magnesium stearate (see preparation in paragraph [0050]) with a tablet obtained from a granulate containing 0.50% by weight of magnesium stearate (paragraph [0051]). The results in figure 1 show that the tablet according to the patent is harder than the comparative tablet (figure 1, paragraph [0051]). In the example according to the patent a granulate compression speed of about 250000 tablets/h is attainable with adequate tablet quality and low machine wear (paragraph [0053]).
- 2.4 From the results of these tests it is clear that the only property which has been compared for a tablet according to the invention and the chosen comparative tablet is the hardness. No data are available for compressing speed, machine wear, tablet rupture and

pharmaceutical properties of the comparative tablet which could render a comparison possible. Already on this basis, the only effect which could be acknowledged in view of the available data is the one on the tablet hardness.

2.5 There are a number of further reason which puts doubts on the suitability of the tests in example 1 in the patent to credibly show effects and advantages of the claimed composition with respect to the product of the closest prior art.

2.5.1 Firstly, it is not clear from the information on the preparation of the two tablets whether the amount by weight of magnesium stearate is the only difference between the two tablets. At least as far as the particle size distribution is concerned, the information given, namely that for the comparative granulate the size distribution is such that more than 50% by volume of the particles are granulate particles with a size of less than 100 μm (paragraph [0051]), while the granulate used for the tablet according to the invention is the one in figure 2 with a clear maximum value around 200 μm , makes it unlikely that the distribution is the same in the two cases. In addition it is not indicated whether all the other features of the two compositions (e.g. the presence and quantity of the other ingredients) are the same for the two tablets. On that basis it is not possible to conclude that any shown effect is related to the identified distinguishing feature. On top of that, it is not known whether the comparative tablet actually corresponds to the product Minirin[®].

2.5.2 Secondly, while the amount of magnesium stearate in the product of the closest prior art (0.50% by weight) is

quite close to the upper value of the range of claim 1 (0.40% by weight), a comparison is made with a tablet having half of the amount of the prior art product (0.25% by weight) which, even in the presence of complete and conclusive results, would raise doubts on whether they can be extrapolated over the whole range of the amount of lubricant covered by claim 1 of the main request.

2.5.3 Finally, the only other example available in the abundant documentation on file, namely example 1 of E18, which in spite of being late published can be considered as experimental evidence provided after filing, shows that a tablet which is produced by a method which is very similar to the one of the product of the invention in example 1 of the patent (compare paragraph [0037] in E18 with paragraph [0050] in the patent), apart from having a quantity of magnesium stearate of 0.50% by weight instead of 0.25% by weight, provides results in terms of compression speed, tablet quality and machine wear which are described with exactly the same wording as for the example in the patent in suit ("a compression speed of about 250000 tablets/h is attainable with adequate tablet quality and low machine wear", compare paragraph [0037] of E18, last but one sentence and paragraph [0053] in the patent). This example raises further doubts that the claimed advantages in compression speed, tablet quality and machine wear may be achieved by means of the reduction in the amount of lubricant.

2.6 While the considerations made above (see in particular points 2.5.1 and 2.5.2) raise doubts even on the relevance of the available data for the effect on tablet hardness, the Board considers that the increase in hardness as a result of a decrease in the amount of

lubricant can be accepted as a credible effect in view of the large number of documents which disclose such a correlation between the amount of lubricant and the tablet hardness (see all the documents cited in paragraph 28 of the reasons of the appealed decision, which for the sake of brevity are not repeated here) and as this effect has not been contested by the appellants.

2.7 With regard to the question of who bears the burden of proof in showing that effects and advantages have been achieved, the case law, in line with the general principle that each of the parties to the proceedings bears the burden of proof for the facts they allege (Case Law of the Boards of Appeal, 7th edition 2013, III.G.5.1.1), has consistently supported the view that alleged advantages to which the patent proprietor merely refers without offering sufficient evidence, supported by any comparison with the closest prior art, cannot be taken into consideration in determining the problem effectively solved by the underlying invention (Case Law, *supra*, I.D.4.2). In the present case therefore, in line with the case law, the burden of proof lies with the respondent, which has not discharged it, as long as advantages with respect to compressing speed, machine wear, tablet rupture and pharmaceutical properties with respect to the product of the closest prior art are concerned.

2.8 On that basis, the problem solved by the composition of claim 1 of the main request with respect to the product Minirin[®] as the closest prior art is the provision of a solid dosage form with increased hardness. This problem has been credibly solved in view of the information on file (see in particular points 2.3, 2.4 and 2.6, above).

3. It remains to be determined whether the proposed measure, namely to decrease the amount of lubricant, is an obvious solution to the posed problem.
- 3.1 It has been a common understanding of the parties, which has also been accepted in the formulation of the solved problem (see point 2.6, above), that it is well known in the art that an increase of the tablet hardness can be obtained by a reduction in the amount of lubricant. With regard to the accepted relationship between the tablet hardness and the lubricant amount, there is no need to add anything to the analysis in the appealed decision, which referred to the common general knowledge and to a large number of documents (see paragraph 28 in the reasons).
- 3.2 The only objection to this line by the respondent was that none of these documents points specifically to a value below the amount of 0.50% by weight and suggests therefore the choice of the specific range given in the claim.
- 3.3 This argument is, however, not considered as convincing by the Board. Given that the product of the closest prior art has 0.50% by weight of lubricant and it is known that an increase in the tablet hardness can be obtained by a decrease in the amount of lubricant, the skilled person, aiming at solving the posed problem, would necessarily choose a value below 0.50% by weight and fall within the range given in claim 1 of the main request without the need of any more specific indication in the prior art, all the more because no specific advantage has been shown for the specific range in the claim.

- 3.4 On that basis, the composition of claim 1 of the main request does not involve an inventive step.

Auxiliary requests I to III - inventive step

4. The features added to claim 1 of auxiliary requests I, II and III, namely that "the solid dosage form is a perorally available tablet" (auxiliary requests I, II and III), that the solid dosage form "comprises desmopressin acetate in an amount of from 20 to 600 µg per tablet" (auxiliary requests II and III) and that the lubricant is "magnesium stearate" (auxiliary request III) do not constitute further differences with respect to the product Minirin[®], as acknowledged by the respondent.
- 4.1 Indeed, the product Minirin[®] is a tablet for oral use, contains 0.1 or 0.2 mg desmopressin acetate and 0.50% by weight magnesium stearate (see E3A and E27).
- 4.2 On that basis, the analysis of inventive step developed for the composition of claim 1 of the main request equally applies to the composition of claim 1 of auxiliary requests I, II and III (see points 1 to 3, above).
- 4.3 As no additional arguments have been provided by the parties with respect to inventive step of claim 1 of auxiliary requests I, II and III, the Board does not need to analyse the issue in any further detail and concludes that the composition of claim 1 of auxiliary requests I, II and III does not involve an inventive step.

Auxiliary request IV - admissibility

5. Auxiliary request IV was filed by the respondent at the oral proceedings before the Board. This request is an amendment of the respondent's case which came not only well after it had filed its reply to the statements of grounds, but actually at the very last opportunity to make submissions. It is therefore under the discretion of the Board to decide whether the request is to be admitted (Article 13(1) of the Rules of Procedure of the Boards of Appeal, RPBA).

5.1 Contrary to the submissions of the respondent the late filing of the request could not be seen as justified by the doubts expressed by the Board in its communication that the data available in the patent provided sufficient evidence for the problem as formulated by the respondent (point VIII, above), as these doubts corresponded to arguments and objections submitted by the appellants with their statements of grounds (point VI, above) and did not introduce any new situation which could justify a reaction.

5.2 Indeed, the possible relevance of the particles size distribution of the tablets in the example and comparative example had been mentioned by the appellants in their statements of grounds and there was no justification for the respondent to wait for over four years and introduce into claim 1 a feature related to the particle size distribution at the very last opportunity.

5.3 Moreover, the added feature, which has never been discussed by the parties as to its relevance to inventive step, raises new questions (e.g. related to which is the particle size distribution of the

granulate of the closest prior art and to which are the differences between the particle size distributions of the granulates of the example and comparative example in the patent) which the appellants could not reasonably be expected to deal with without adjournment of the oral proceedings (Article 13(3) RPBA).

- 5.4 Under these circumstances, the Board can see no justification for the respondent to introduce the new request at such a late stage of the proceedings and the Board on exercise of its discretion under Rule 13 RPBA finds it appropriate not to admit auxiliary request IV into the proceedings.

Conclusions

6. As all requests which are admitted into the appeal proceedings fail for lack of inventive step, there is no need for the Board to decide on any other issue and the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated