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Datasheet for the decision of 3 November 2015

Case Number: T 0498/11 - 3.3.07

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Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL FORMULATION OF OLANZAPINE

Patent Proprietor:
KRKA, tovarna zdravil, d.d., Novo mesto

Opponents:
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White, Nina Louise
STRAWMAN LIMITED
LUDWIG, Gabriele

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12

Keyword:
Inventive step - (no)
Admission of auxiliary requests (yes)

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Case Number: T 0498/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 November 2015

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 29 December 2010 revoking European patent No. 1558219 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: R. Hauss
P. Schmitz

Summary of Facts and Submissions

I. European patent No. 1 558 219 was granted on the basis of sixteen claims.

Independent claim 1 reads as follows:

"1. A pharmaceutical formulation comprising olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient, obtainable by homogeneously mixing
(a) olanzapine or a pharmaceutically acceptable salt thereof with
(b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidised form thereof,
(c) a polysaccharide
and optionally one or more additional excipients,
followed by a direct compression of the mixture into tablets in the absence of any solvent."

II. The patent was opposed by seven opponents under Articles 100(a), (b) and (c) EPC 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.

III. The documents cited in the opposition and appeal proceedings included the following:

D1: EP-A-0 830 858

D2: Zyprexa/Zyprexa Zydis; http://web.archive.org/web/*/http://www.fda.gov/cder/approval/index.htm, retrieved 30 March 2007, Eli Lilly and Company, 1997, 2000

D3: Zyprexa®, Extract from the ABPI Compendium of Data Sheets 1999-2000

D4: EP-A-0 454 436

D5: EP-A-0 733 367

D7: WO-A-98/11897

D11: Remington: The Science and Practice of Pharmacy, 19th ed., Easton 1995, pages 1609-1611; 1615-1619; 1626-1627

D13: Eur. J. Pharm. Biopharm. 42(5), 325-330 (1996)

D14: "Direct compression tableting", Encyclopedia of pharmaceutical technology, Ed. Swarbrick, Boylan, Vol. 4, Marcel Dekker 1991, pages 85-106

D18: "Cellactose, ein neuer Hilfsstoff für die Herstellung fester Arzneiformen - Eigenschaften und Möglichkeiten", E. Reimerdes, Vortrag auf der ZDS-Tagung in Solingen; 25-27 February 1991

D21: EP-A-0 503 521

IV. With letter of 10 February 2009 opponent 4 withdrew its opposition.

V. The appeal lies from the decision of the opposition division, announced on 14 October 2010 and posted on 29 December 2010, revoking the patent. The decision was based on the claims as granted.

In the decision under appeal the opposition division considered that the subject-matter of claim 1 lacked inventive step over document D4 as closest prior art, in combination with D13 or D18. The formulation defined in claim 1 differed from example formulation 4 of D4 in the presence of ingredient (b). The effect of the difference was demonstrated in examples 1 and 2 of the patent, which showed that formulations comprising Cellactose® (a specific spray-dried and agglomerated mixture of 75 weight % α-lactose monohydrate and 25 weight % cellulose powder, hereinafter: "cellactose") were more stable than corresponding formulations not

containing lactose. The objective technical problem was the provision of a further pharmaceutical formulation of olanzapine obtained by direct compression with improved storage stability. The use of lactose as an excipient in formulations of olanzapine was already mentioned in D4, and lactose was a commonly used tablet filler. In view of D13 or D18, which disclosed that cellactose provided certain advantages over other excipients, the skilled person, without exercising inventive skill, would have considered employing it instead of cellulose in example 4 of D4 in order to solve the technical problem. As such, claim 1 as granted did not meet the requirements of Article 56 EPC.

VI. The appellant (patent proprietor) lodged an appeal against that decision. With the statement setting out the grounds of appeal the appellant stated that its **main request** was the maintenance of the patent in the form as granted, while the first to fifth auxiliary requests were identified as those submitted in opposition proceedings with letter of 13 August 2010.

Independent claim 1 of the **first auxiliary request** differs from claim 1 as granted by the addition of the following text: *"... , wherein the polysaccharide is selected from the group consisting of starch, cellulose, and mixtures thereof".*

Independent claim 1 of the **second auxiliary request** differs from claim 1 as granted by the addition of the following text: *"... , wherein the pharmaceutical formulation comprises 40 to 80 weight % of the component (b) and 10 to 40 weight % of the polysaccharide".*

Independent claim 1 of the **third auxiliary request** differs from claim 1 as granted by the addition of the following text: *"... , wherein component (b) is lactose and the polysaccharide is cellulose".*

Independent claim 1 of the **fourth auxiliary request** differs from claim 1 as granted by the addition of the following text: *"... , wherein the tablets do not contain microcrystalline cellulose".*

Independent claim 1 of the **fifth auxiliary request** differs from claim 1 as granted by the addition of the following text: *"... and without any coating".*

VII. The respondents (opponents) 1, 2, 3, 6 and 7 replied to the appellant's statement of grounds and submitted arguments.

VIII. The board issued a summons to oral proceedings.

IX. In response to the summons, respondent-opponent 2 subsequently withdrew its opposition.

X. In a communication issued in preparation for oral proceedings, the board summarised the issues and noted in particular that in respect of inventive step, document D7 appeared to represent a suitable starting point for the skilled person.

Furthermore, the board expressed the preliminary opinion that if the technical problem were to be seen as merely the provision of a further olanzapine tablet formulation, the proposed tablet formulation incorporating a component (b) would appear to constitute an arbitrary choice for the skilled person.

Finally, the board expressed doubt as to whether the technical effect of improved stability, if recognised for the examples of the patent, could be considered

achievable across the entire scope of claim 1 of the main request.

XI. Oral proceedings were held on 3 November 2015.

XII. The appellant's arguments, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step of claim 1

a) Document D7 was a suitable starting point for the skilled person. The formulation defined in claim 1 differed from formulation 2 of D7 in that it additionally comprised ingredient (b). The effect was demonstrated in the patent specification, according to which the composition of *Referential example 1*, which resembled formulation 2 of D7 and could therefore be seen as representative thereof, was less stable than that of example 2, which comprised cellactose.

b) The results obtained by employing cellactose constituted sufficient evidence for demonstrating the technical effect of the presence of component (b) over the entire claimed scope, since although cellactose possessed specific physical characteristics by virtue of its preparation, the latter only influenced the *physical* characteristics of the tablet, while it was the *chemical* characteristics which were important for the desired stability, the latter being the same for a mere mixture of lactose and cellulose. Although only demonstrated for the combination of lactose (component (b)) and cellulose (component (c)) according to example 2 of the patent, the effect was also plausible for other monosaccharides and polysaccharides, since the specific components chosen for said example were the most frequently employed in the field. Furthermore, none of the seven opponents had

demonstrated that an alternative combination of components (b) and (c) would not improve stability.

c) The objective technical problem was thus the provision of a more stable composition comprising olanzapine.

d) The solution to that problem as set out in claim 1 was not obvious over the disclosure of D7 itself. Although lactose was mentioned therein as a single member of a list of typical diluents (page 18, lines 12-16), there was no motivation for the skilled person to choose this specific excipient with a view to solving the problem.

e) The argument that the skilled person would have employed cellactose in order to solve the technical problem, particularly in view of the known advantageous properties thereof, was based on hindsight. The skilled person knew from document D14 (page 97, last paragraph), which represented the common general knowledge, that microcrystalline cellulose was an excipient whose properties were "not far from optimal", and thus would not have considered that formulation 2 of D7, which comprises microcrystalline cellulose, could be further improved upon.

f) The skilled person knew from his common general knowledge (see D11, page 1617, right hand column, paragraph 1) that lactose may form impurities with amines via the Maillard reaction. Since olanzapine was an amine comprising four nitrogen atoms, the skilled person wishing to avoid undesired discoloration would have avoided the use of lactose.

g) Even if the effect of improved stability were not to be recognised, and the objective technical problem were

to be formulated as the provision of a further composition comprising olanzapine, the solution to the problem of providing a further composition comprising olanzapine would not have been obvious to the skilled person, for the same reasons as those provided above according to points d), e) and f).

h) For these reasons, claim 1 of the main request involved an inventive step.

Admission of the auxiliary requests

The five auxiliary requests, re-introduced with the statement setting out the grounds of appeal, had been withdrawn in opposition oral proceedings in view of the understanding that the opposition division considered the preferred embodiments according to said requests to be obvious from the prior art. As a consequence, the patent proprietor did not see any reason to further discuss these requests at the oral proceedings.

Auxiliary requests - inventive step of claim 1

The same arguments in respect of inventive step applied to claim 1 of each of the auxiliary requests. In addition, claim 1 of the second auxiliary request was limited to the preferred weight percentage ranges of components (b) and (c) within which the best technical effect could be achieved (as illustrated by examples 2 and 3 of the patent), and the formulation according to claim 1 of the fourth auxiliary request further differed from formulation 2 of D7 by the exclusion of microcrystalline cellulose, said to be disadvantageous according to the patent specification (paragraph [0022]).

XIII. The respondents' arguments, as far as relevant to the present decision, can be summarised as follows:

Main request - inventive step of claim 1

Starting from formulation 2 of document D7, the difference with respect to claim 1 of the main request was that noted by the appellant, viz. component (b).

No data had been provided demonstrating the alleged technical effects of dose uniformity and less discoloration, while ease of preparation provided by direct compression had already been demonstrated in D7, formulation 2.

The effect of formulation stability demonstrated for cellactose, a special excipient prepared in a specific way and having specific properties, was not plausible across the scope of the claim, even for a mere mixture of lactose and cellulose. In this regard, the burden of proof lay with the appellant.

The objective technical problem was the provision of an alternative olanzapine-containing tablet prepared by direct compression, and the solution was obvious in view of the prior art, specifically document D7 itself, which referred to the possibility of employing lactose, and i.a. documents D13 and D21, which disclosed the advantageous properties of cellactose, thereby providing sufficient incentive for the skilled person to consider employing it.

Furthermore, the skilled person would not be deterred by concerns that lactose would undergo a Maillard reaction with olanzapine, since the latter possessed sterically hindered ring nitrogen atoms which the skilled person would not expect to be reactive.

Admission of the auxiliary requests

The five auxiliary requests filed with the statement setting out the grounds of appeal were identical to those which were once put forward but subsequently withdrawn during oral proceedings before the opposition division, with the result that the opposition division was prevented from providing a reasoned decision on the critical issues at hand. This constituted an abandonment of the proprietor's right to have said auxiliary requests considered by two instances.

Auxiliary requests - inventive step of claim 1

The same arguments applied as for claim 1 of the main request. No effect had been demonstrated with respect to the limited percentage ranges according to claim 1 of the second auxiliary request, nor with respect to the exclusion of microcrystalline cellulose from the scope of claim 1 of the fourth auxiliary request, such that the arguments remained the same for these requests, too.

XIV. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted, or alternatively that the patent be maintained on the basis of one of the first to fifth auxiliary requests filed in opposition proceedings with the letter of 13 August 2010.

XV. The respondents requested that the appeal be dismissed. Respondent-opponent 6 additionally requested that the auxiliary requests not be admitted into the proceedings.

Reasons for the Decision

1. Main request - inventive step of claim 1

Patent in suit

1.1 Olanzapine is a neuroleptic with relaxant, anxiolytic or antiemetic properties; it is moisture-sensitive and metastable (see paragraphs [0002] and [0003] of the patent specification). The patent in suit seeks to provide a stable solid formulation thereof, without any undesired discoloration or poor dose uniformity, which can be prepared by a simple and economical process (paragraph [0004]). The patent and the application as filed mention documents D1, D7 and the B1 publications corresponding to documents D4 and D5 as relevant prior art.

Starting point in the prior art

1.2 The appellant disagreed with the choice of D4 as the closest prior art in the decision under appeal and submitted that either D1 or D5 served as more appropriate starting points for the assessment of inventive step. In the preliminary opinion sent in preparation for oral proceedings (see point X. above and the board's preliminary opinion, point 6.1.3), the board shared the opinion of respondent-opponent 6 (set out in the letter of 12 September 2011, point 2.2.2) that D7 represented a suitable starting point for the skilled person. During oral proceedings before the board, the appellant did not contest the suitability of D7 as a starting point, and presented arguments in favour of inventive step on the basis of D7. Thus, irrespective of whether further documents such as D1, D4 or D5 may also be suitable for this purpose, D7 may

be chosen as a starting point for the assessment of inventive step.

1.3 D7 discloses a tablet (formulation 2) prepared by direct compression, which contains olanzapine, fluoxetine hydrochloride, microcrystalline cellulose, silicon dioxide and stearic acid. Since claim 1 as granted does not exclude the presence of further pharmaceutically active ingredients such as fluoxetine, the only difference between the tablets of claim 1 and those of D7 is the mandatory presence of component (b), i.e. a monosaccharide and/or oligosaccharide and/or a reduced or oxidised form thereof.

Technical problem and solution

1.4 In order to formulate the technical problem effectively solved by the claimed subject-matter, it must be determined whether the distinguishing features of the claim credibly provide the alleged technical effects or advantages over the entire claimed scope.

1.5 Starting from the disclosure of document D7, the appellant has defended only the effect of increased stability, on the basis of the evidence provided by the examples of the patent specification. No evidence has been provided supporting the alleged effects of prevention of undesired discoloration or poor dose uniformity, while the preparation of the formulation by the simple and economical process of direct compression is already disclosed in formulation 2 of D7.

1.6 The evidence provided in the patent specification itself in support of the technical effect of increased stability is derived from reference example 1, and examples 2 and 3 representing the invention. According to the reported test results, when subjected to

stability testing (1 month, 40°C/75% relative humidity, open air), the olanzapine tablet formulation of example 2 (according to the invention) comprising cellactose showed an increase in "total related compounds" from 0.40% to 1.63%, while the corresponding formulation comprising microcrystalline cellulose in the absence of lactose (example 1) showed an increase from 0.49% to 3.40% thereof. The parameter "total related compounds" is meant to reflect the level of impurities formed by chemical degradation. Since the formulation of example 1 is similar to formulation 2 of D7, it can be accepted that example 1 is adequately representative of the prior art D7. Thus, the effect of increased stability is demonstrated for the formulation of example 2 of the patent in suit. (Example 3 does not provide any additional information, since it also uses cellactose to represent a mixture of components (b) and (c), but several parameters differ in a comparison of examples 3 and 1).

1.7 It remains to be determined whether the technical effect demonstrated for example 2 of the patent can be considered plausible across the entire scope of claim 1.

1.8 As pointed out by the respondents, the patent only comprises two examples according to the invention (examples 2 and 3), both of which employ a specific mixture of lactose and cellulose in the form of cellactose. As already mentioned (see point V. above), cellactose is a spray-dried and agglomerated granular composition of 75 weight % of alpha-lactose monohydrate and 25% cellulose powder (see the patent in suit: paragraph [0023]; D13: page 325, left hand column, paragraphs 1 and 2; D21: page 5, lines 28 to 30). According to D13 (see page 325: summary and

introduction) cellactose has special properties attributable not only to the specific combination ratio of the ingredients, but also to the method in which this substance is co-processed and agglomerated.

1.9 Thus cellactose is not a typical tableting excipient, as it is not merely a mixture of lactose and cellulose. The board does not consider it credible that, as alleged by the appellant, a clear line of separation can be drawn between on the one hand the *physical* characteristics and on the other hand the *chemical* characteristics of cellactose by virtue of its method of preparation. Even if it were to be accepted that the difference between cellactose and a mere mixture of lactose and cellulose were to be considered purely physical, these differences may still have (indirect) chemical consequences in terms of the reactivity of the active agent (and thus its propensity to form "related compounds"). Furthermore, the alleged advantages of the combined use of components (b) and (c) recited in the patent specification (see paragraph [0027]) are identical to those assigned to cellactose according to D13 (improved compactability, flow characteristics and tablet strength). According to D13 (page 325, left hand column, second paragraph), cellactose may form interactive mixtures with active ingredients and may have improved flow and packing characteristics. Cellactose is also said to improve bonding ability, resulting in stronger tablets (D13, page 330, left hand column, lines 1-4). In this context, it may well be the case that these *physical* characteristics may have *chemical* implications, and play a role in, for example, the accessibility and thus the susceptibility of the water-sensitive active agent olanzapine to water. It is not implausible to imagine, for example, that increased tablet strength or improved packing characteristics

attributable to the physical characteristics of cellactose may affect the water permeability of the tablet, or that olanzapine and cellactose may form "interactive mixtures" which play a role in protecting the active agent.

1.10 The appellant has furthermore submitted in arguing inventive step that none of the seven opponents had demonstrated that an alternative combination to those of examples 2 or 3 of the patent would not improve stability. However, since there are good reasons for the assumption that cellactose used in examples 2 and 3 may have untypical properties (see points 1.8 and 1.9 above), the burden of proof lies with the appellant who has alleged that improved stability is achievable across the entire scope of the claim. This objection was raised as early as the filing of the notices of opposition, such that the appellant had sufficient opportunity to counter it by filing further evidence.

1.11 Furthermore and independently, the board does not consider it plausible that the effect demonstrated exclusively for a mixture of 75 weight % alpha-lactose monohydrate and 25 weight % cellulose powder (paragraph [0025]) can be extrapolated to the same mixture in all possible combination ratios, meaning that for this reason, too, the effect cannot be extrapolated across the entire scope of the claim.

1.12 Consequently, while the technical effect of improved stability has been demonstrated for a tablet according to claim 1 comprising cellactose as ingredients (b) and (c), it cannot be considered achievable across the entire scope of claim 1.

1.13 In view of these considerations, the board holds the technical problem to be the provision of a further composition comprising olanzapine.

1.14 The board is satisfied that the problem has been solved by the claimed tablet formulation which incorporates component (b), i.e. a monosaccharide and/or oligosaccharide and/or a reduced or oxidised form thereof.

Obviousness

1.15 To solve the problem of providing an alternative to the composition of formulation 2 of D7, it would be an arbitrary choice for the skilled person to choose to add to or replace the excipients employed with those known in the art. D7 itself lists lactose as one such excipient (page 18, line 18), while D13 teaches that cellactose is a suitable excipient combination, especially in the context of the production of tablets by direct compression.

1.16 Furthermore, the board does not consider as credible the appellant's view that concerns about an undesirable Maillard reaction represented a serious disincentive which would prevent the skilled person from considering lactose as a suitable excipient. Olanzapine contains four ring nitrogen atoms, only one of which possesses a lone pair of electrons. In addition to being secondary, this nitrogen atom is part of a condensed heterocyclic ring system and will be at least sterically hindered to the degree that the skilled person with general chemical knowledge, in the absence of any evidence to the contrary, would not consider susceptibility to the Maillard reaction as a concern. Furthermore, lactose is present in the known olanzapine compositions of the

prior art according to D5 (example 1), D2 and D3, indicating that it was not considered unsuitable.

1.17 It follows that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

2. Admission of the auxiliary requests

2.1 The first to fifth auxiliary requests introduced with the statement setting out the grounds of appeal are identical to the auxiliary requests which were withdrawn during oral proceedings before the opposition division. The respondents were of the view that therefore the auxiliary requests should not be admitted into the appeal proceedings.

2.2 Article 12(4) RPBA gives the board discretion not to admit requests which could have been presented before the first instance. When exercising its discretion the board has to take into account all factors relevant to the case.

2.2.1 The board's primary task is to review the first instance decision and to give a judicial ruling on whether that decision was correct. By withdrawing the auxiliary requests the appellant prevented the department of first instance from giving a reasoned decision on those requests.

2.2.2 On the other hand however, the technical features added in the auxiliary requests did not change the factual basis of the appeal proceedings. This is reflected in the fact that, with regard to the auxiliary requests, the parties referred basically to the arguments they had relied on in the discussion of the main request, with few additions. Nor did the board have any

difficulty in examining the auxiliary requests without a reasoned decision of the opposition division.

2.3 Balancing these factors, the board sees no reason for not admitting the auxiliary requests into the appeal proceedings.

3. First auxiliary request - inventive step of claim 1

3.1 According to claim 1 of the first auxiliary request, the mandatory polysaccharide component (c) has been limited to starch, cellulose and mixtures thereof.

3.2 Since there is thus no further differentiating feature over formulation 2 of D7, the subject-matter of claim 1 does not involve an inventive step for the same reasons as those provided for claim 1 of the main request (see points 1.1 to 1.17 above).

4. Second auxiliary request - inventive step of claim 1

4.1 According to claim 1 of the second auxiliary request, components (b) and (c) are each specified to fall within a certain percentage weight range.

4.2 While this constitutes a further difference with respect to formulation 2 of D7 in that the amount of microcrystalline cellulose in the latter falls outside the claimed range, no evidence has been presented which would indicate a technical effect arising from the difference, such that the technical problem remains the same as that identified for claim 1 of the main request.

4.3 The solution to that problem as defined in claim 1 of the second auxiliary request, including the arbitrary choice of known excipients in weight ranges which are

standard in the art, does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as those provided for claim 1 of the main request (see points 1.1 to 1.17 above), and because the merely arbitrary choice of a concentration range of component (c) cannot contribute anything to inventive activity.

5. Third auxiliary request -inventive step of claim 1

5.1 According to claim 1 of the third auxiliary request, ingredients (b) and (c) have been limited to lactose and cellulose respectively.

5.2 Since there is thus no further differentiating feature over formulation 2 of D7, the subject-matter of claim 1 does not involve an inventive step, for the same reasons as those provided for claim 1 of the main request (see points 1.1 to 1.17 above).

6. Fourth auxiliary request - inventive step of claim 1

6.1 According to claim 1 of the fourth auxiliary request, the tablets do not contain microcrystalline cellulose.

6.2 Since formulation 2 of D7 comprises microcrystalline cellulose, this constitutes a further distinguishing feature with respect to the closest prior art. However, "powdered cellulose derivatives" and "celluloses" are mentioned in a list of possible excipients according to D7 (page 18, lines 15-16 and 30). Since no evidence is on file demonstrating an effect linked to the absence of microcrystalline cellulose, the technical problem as formulated for claim 1 of the main request remains the same. The solution to that problem as defined in claim 1 of the fourth auxiliary request remains an arbitrary selection from the possible excipients listed

in D7 and consequently lacks an inventive step for the same reasons as those provided for claim 1 of the main request (see points 1.1 to 1.17 above).

7. Fifth auxiliary request - inventive step of claim 1

7.1 Claim 1 of the fifth auxiliary request stipulates that the claimed formulations are prepared "without any coating".

7.2 Since formulation 2 of D7 is prepared without any coating, there are no further differentiating features, and the subject-matter of claim 1 does not involve an inventive step, for the same reasons as those provided for claim 1 of the main request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated