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Datasheet for the decision of 4 March 2014

Case Number: T 1420/10 - 3.3.07

Application Number: 03771910.1

Publication Number: 1539115

IPC: A61K9/24, A61K31/506, A61P25/18

Language of the proceedings: EN

Title of invention:
METHODS AND DOSAGE FORMS FOR CONTROLLED DELIVERY OF PALIPERIDONE

Patent Proprietor:
ALZA Corporation

Opponent:
Hexal AG

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main request (no) - auxiliary request (no)

Decisions cited:

Catchword:

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Case Number: T 1420/10 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 March 2014

Appellant: (Patent Proprietor)	ALZA Corporation 1900 Charleston Road, P.O. Box 7210 Mountain View, CA 94039-7210 (US)
Representative:	Williams, Paul Edwin Ablett & Stebbing 7-8 Market Place London W1W 8AG (GB)
Appellant: (Opponent)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Wittkopp, Alexander Maiwald Patentanwalts GmbH Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 April 2010 concerning maintenance of the European Patent No. 1539115 in amended form.**

Composition of the Board:

Chairman: J. Riolo
Members: D. Semino
D. T. Keeling

Summary of Facts and Submissions

I. The appeals of the patent proprietor and of the opponent lie against the decision of the opposition division announced at the oral proceedings on 25 March 2010 to maintain European Patent 1 539 115 as amended.

II. A notice of opposition was filed against the granted patent requesting revocation of the patent in its entirety on the ground of lack of inventive step in accordance with Article 100(a) EPC.

III. During opposition proceedings the following documents *inter alia* were cited:

D8: WO-A-00/54764
D9: WO-A-99/62496
D10: Affidavit/Declaration of Dr. Peter Lewyn-Briscoe dated 2 January 2009 filed by the patent proprietor with letter of 4 February 2009

IV. The decision was based on two sets of claims filed with letter of 25 January 2010 as main request and first auxiliary request and on a further set of claims filed as second auxiliary request during oral proceedings on 25 January 2010.

Claim 1 according to the main request read as follows:

"1. An oral dosage form for once-a-day administration, comprising:
two or more layers, said two or more layers comprising a first layer and a second layer, said first layer comprises paliperidone, risperidone or a pharmaceutically acceptable salt thereof, said second layer comprises a polymer; an outer wall surrounding

said two or more layers; and an orifice in said outer wall;
wherein said dosage form maintains an ascending release rate of said paliperidone, risperidone or pharmaceutically acceptable salt thereof over a continuous period of at least 8 hours."

The condition on the ascending release rate was introduced in claim 1 of the main request with respect to claim 1 as granted. In claim 1 of the first auxiliary request that condition was more specifically defined as "wherein said dosage form maintains an ascending release rate of said paliperidone, risperidone or pharmaceutically acceptable salt thereof, in that the average hourly release rate increases over the immediately-preceding average hourly release rate, over a continuous period of at least 8 hours".

Claim 1 of the second auxiliary request read as follows:

"1. An oral dosage form for once-a-day administration, comprising:
two or more layers, said two or more layers comprising a first layer and a second layer, said first layer comprises paliperidone or a pharmaceutically acceptable salt thereof, said second layer comprises a polymer; an outer wall surrounding said two or more layers; and an orifice in said outer wall;
wherein said second layer further comprises paliperidone or a pharmaceutically acceptable salt thereof, and wherein the ratio of the amount of paliperidone or a pharmaceutically acceptable salt thereof in said first layer to the amount of paliperidone or a pharmaceutically acceptable salt

thereof in said second layer is less than 1.0 to thereby maintain an ascending release rate of said paliperidone or pharmaceutically acceptable salt thereof over a continuous period of at least 8 hours."

All requests included a second independent claim formulated as a second medical use claim in the Swiss form.

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

a) The main request and the first auxiliary request did not fulfill the requirements of Article 84 EPC having regard to the functional definition introduced in claim 1.

b) As to the second auxiliary request, the limitation related to the ratio of the amount of drug in the two layers in claim 1 did not result in any added subject-matter. The requirement of sufficiency was met in the light of the examples and the instructions given in the description and of the structural features of claim 1. All essential structural features were present in claim 1, so that also the requirements of Article 84 EPC were met.

c) As far as inventive step was concerned, document D8 had to be taken as the closest prior art. The differences with respect to claim 1 were the specific active principle and the layer structure with a specific concentration gradient. The problem solved was the provision of a dosage form for paliperidone with an ascending release rate for at least 8 hours. The solution was inventive,

as there was no incentive for the skilled person to apply the dosage forms of document D9 to paliperidone. An analogous reasoning could be applied to the second medical use claim.

VI. Both parties lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant-patent proprietor defended the main request and the first auxiliary request on which the appealed decision was based with respect to the requirements of Article 84 EPC.

VII. In a communication sent in preparation of oral proceedings the Board, with regard to inventive step, observed *inter alia* that both in the decision under appeal and in the arguments of the parties document D8 had been chosen as the closest prior art and did not see any reason to choose a different starting point (paragraph 2.1). In addition the Board expressed its doubts that the tests in D10 might provide sufficient evidence concerning effects or advantages of the claimed dosage form with respect to that of the closest prior art (paragraph 2.4).

VIII. With letter of 28 February 2014 the appellant-patent proprietor withdrew the previous main and first auxiliary requests, replaced the previous main request with the previous second auxiliary request and filed a further set of claims as auxiliary request. Claim 1 of the auxiliary request read as follows:

"1. An oral dosage form for once-a-day administration, comprising:
an outer wall being a membrane defining a compartment, at least a portion of the outer wall being semipermeable;

an exit orifice in the outer wall;
an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of said outer wall;
a first drug layer located within the compartment and adjacent the exit orifice; and
a second drug layer located within the compartment between the first drug layer and the expandable layer;
wherein said first drug layer and said second drug layer comprise paliperidone or a pharmaceutically acceptable salt thereof, and said second drug layer comprises a polymer;
and wherein the ratio of the amount of paliperidone or a pharmaceutically acceptable salt thereof in said first drug layer to the amount of paliperidone or a pharmaceutically acceptable salt thereof in said second drug layer is less than 1.0; to thereby maintain an ascending release rate of said paliperidone or pharmaceutically acceptable salt thereof over a continuous period of at least 8 hours."

IX. Oral proceedings were held on 4 March 2014.

X. The arguments of the appellant-patent proprietor, as far as relevant to the present decision, can be summarised as follows:

Inventive step

a) Document D8, which was considered as the closest prior art in the appealed decision, dealt with the treatment of bulimia and provided a very general disclosure of any possible dosage form, but gave as the only specific example an immediate release dosage of 1.5 mg risperidone to be given at bedtime. The product of claim 1 of the set of

claims on which maintenance of the patent was based in the appealed decision differed from those disclosed in D8 in the structure of the dosage form and in that it maintained an ascending release rate over a period of at least 8 hours. The presence of paliperidone was in principle a further distinguishing feature, but such an active compound was therapeutically equivalent to risperidone and the two active compounds were interchangeable with regard to the claimed invention.

b) The effects obtained by such differences were the reduction in side effects without the need of titration and an improvement in efficacy. The tests in D10 showed that these effects were actually obtained. The Phase 1 study compared a treatment according to D8 (risperidone administered with titration) with a treatment using the dosage form of the invention without titration and showed that the latter was non-inferior to the former in side effects, which one would not expect in the absence of titration. The Phase 3 study in D10 showed that the claimed dosage form was more effective than one would expect by comparing treatment with the claimed dosage form at different quantities of paliperidone against an approved treatment with olanzapine. In this respect it was relevant to note that the INVEGA product was available on the market, fell under the claimed dosage form and did not include any other hidden ingredient or feature which could be responsible of the advantages. Moreover, 12 mg INVEGA paliperidone which was approximately equivalent to 4 mg immediate response risperidone was expected to induce

orthostatic hypotension as side effect if administered without titration and 3 mg INVEGA paliperidone which was approximately equivalent to 1 mg immediate response risperidone was expected to be sub-therapeutic. The problem was therefore the provision of a dosage form with reduced side effects when administered without titration and improved efficacy.

c) There was no hint in the prior art that a known osmotic dosage form with ascending release rate over at least 8 hours, such as the one of document D9, would solve the posed problem. As the skilled person would not combine the teachings of D8 and D9 without knowledge of the invention, an inventive step should be acknowledged for the product of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision.

d) The same arguments equally applied to the product of claim 1 of the auxiliary request.

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

Inventive step

a) The product of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision differed from the one disclosed in document D8, which represented the closest prior art, in the specific osmotic dosage form with an ascending release rate over a period of at least 8 hours.

b) It was not tenable that advantages were obtained by the choice of administering paliperidone in the specific dosage form. In the application as filed and in the patent possible advantages were only alleged with no tests. The tests in D10 were not relevant, as they did not provide a proper comparison with the closest prior art as required by the case law, according to which the comparative tests should convincingly show that the alleged effects and advantages have their origin in the distinguishing features. The Phase 1 study compared treatment using different drugs in different forms and different quantities, so that it could not be established to which features the alleged advantages could be attributed. The use of paliperidone, which might be therapeutically equivalent to risperidone, but differed therefrom from a pharmacokynetic point of view, could be in itself the cause of the effects instead of the dosage form. The administration of the medicament was also different and it was not clear whether the INVEGA product possessed other features which could be responsible of the alleged advantages. Also the effects of the different quantities and of the absence of a titration on the first day could not be estimated. The Phase 3 study did not provide a comparison with a product according to D8 and was therefore also not suitable to show any effect. In the absence of effects, the problem was simply the provision of a further composition with respect to the one of D8.

c) The skilled person seeking to solve that problem would not need any specific motivation to use the well known dosage form of document D9, which

included the osmotic structure and maintained the desired ascending release rate, all the more as antipsychotic drugs were explicitly mentioned in D9. The use of the dosage form of D9 for a therapeutic equivalent of the medicament of D8 would lead to the product of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision without the involvement of any inventive step.

d) The same arguments equally applied to the product of claim 1 of the auxiliary request.

XII. The appellant-patent proprietor requested that the opponent's appeal be dismissed (main request) or that the patent be maintained on the basis of the amended claims filed by letter of 28 February 2014 (auxiliary request).

XIII. The appellant-opponent requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request - inventive step

1. Document D8 has been chosen as the closest prior art both in the decision under appeal and in the arguments of the parties. The Board does not see any reason to diverge from the approach taken in the decision and by the parties.

1.1 D8 relates to the treatment of eating disorders through the use of antipsychotic medications, in particular risperidone at a dosage of 0.1 to 4.0 milligrams per day (page 6, lines 10 to 21). The dosage can be

administered in any form suitable to the patient, including, but not limited to, oral, intramuscular, rectal and transdermal dosage forms, or other forms known in the art. The dosage form may also be selected from the group consisting of sustained release forms, controlled release forms, delayed release forms and response release forms (page 6, lines 25 to 29). In example 1 treatment is initiated at 0.5 mg twice per day of risperidone and after two weeks the dosage is changed to 1.5 mg to be given at bedtime (page 9, lines 21 to 25).

1.2 The dosage form of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision differs from the one disclosed in D8 in that it contains paliperidone instead of risperidone as the medicament and has a specific layered structure (an outer wall with an orifice and two drug layers with a ratio of the amounts of drug in the first and second layer less than 1.0) to maintain an ascending release rate of paliperidone over at least 8 hours.

1.3 As to the replacement of risperidone with paliperidone, both parties acknowledged that it is well known that the two medicaments are therapeutically equivalent and can be interchanged.

1.4 The parties were in agreement as regards the outlined analysis of D8, the determination of the differences between D8 and the dosage form of the patent in suit and the considerations on the replacement of risperidone with paliperidone. Hence, there is no need to analyse these issues in further detail.

2. The disputed issue which is crucial in the formulation of the solved problem and in the analysis of inventive

step resides in the determination of whether the formulation of paliperidone in a specific dosage form with a specific ascending release rate results in effects and advantages for which convincing evidence has been provided.

2.1 According to the patent the problem is the provision of "effective dosing methods, dosage forms and devices that will permit the controlled release of paliperidone and related compounds over a prolonged period of time at a substantially ascending rate of release to reduce the amount of the active agent that the patient is exposed to at any particular time and to increase the time between dosing, preferably to obtain a once-a-day dosing regimen while reducing associated side effects" (paragraph [0033]). In particular, it is alleged that the specific profile "best provides efficacious therapy over 24 hours while potentially reducing negative side effects associated with administration of the drug" (paragraph [0035]).

2.2 The patent itself does not provide any comparative examples to show a reduction in side effects and an improvement in drug efficacy; the only two examples available (paragraphs [0155] to [0170]) concern the preparation of the dosage form without any testing thereof.

2.3 It remains to be checked therefore whether the only tests available on file, namely the ones in the declaration D10, show that effects and advantages are obtained with respect to the known formulations. These tests include a Phase I Study (Exhibit I of D10, pages 8 to 12) and a Phase III Clinical Trial of Sustained Release (Exhibit II of D10, pages 13 to 19).

2.3.1 The Phase I Study was meant to compare the tolerability of extended-release paliperidone with immediate-release risperidone in subjects with schizofrenia (page 8, first paragraph). The primary objective of the study was a non-inferiority comparison of the orthostatic tolerability (page 8, second paragraph, first sentence). For this purpose two treatments were compared, namely one with extended-release paliperidone at 12 mg per day for six days and one with immediate-release risperidone at 2 mg on the first day and at 4 mg for the subsequent five days (page 8, "Methodology", second and third bullet points). On the basis of the comparison the conclusion was reached that the extended-release paliperidone treatment was non-inferior to the immediate-release risperidone treatment with respect to initial orthostatic tolerability in subjects with schizofrenia (page 12, first sentence).

2.3.2 There are a number of reasons why these tests cannot be considered as appropriate evidence that a reduction in side effects has been proven for the claimed dosage form with respect to the ones of D8.

2.3.3 Firstly, while document D8 discloses generic sustained release and controlled release forms, the tests in D10 do not show that the specific sustained release form with an osmotic dosage form and an ascending release rate over at least 8 hours has an impact on the results with respect to other sustained release forms.

2.3.4 Secondly, the immediate-release risperidone is administered with a titration period of one day and the extended-release paliperidone is administered without titration with no indication of what the effects of that further difference may be. In this respect there

is no evidence to support the assertion that side effects should take place without titration over several days (see e.g. page 4, paragraph 18).

2.3.5 In addition, a different dosage is taken for the two administration forms (12 mg vs 4 mg) based on the contention that the two quantities are approximately equivalent, due to the fact that not all the paliperidone of the extended-release form is absorbed (pages 4 and 5, paragraph 20). Once again the assertion is not supported by evidence (the fact that not all the paliperidone is absorbed is not in itself sufficient to justify a three-fold increase in quantity) and the effects of the difference in quantity are not known.

2.3.6 In any case, the result of the comparison is not a reduction in side effects, but a non-inferiority with respect to a specific tolerability.

2.3.7 On that basis, a reduction in side effects for the claimed dosage form with respect to the dosage forms of D8 cannot be acknowledged.

2.3.8 In the Phase III Clinical Trial of Sustained Release five parallel groups were treated with a placebo, extended-release paliperidone at 3 mg, 9 mg and 15 mg and olanzapine at 10 mg (page 13, first paragraph). According to the appellant-patent proprietor, these tests were meant to show the improved efficacy of the claimed dosage form. As far as efficacy was concerned, the result of these tests was that the improvement in efficacy in all paliperidone treatment groups reached statistical significance when compared to the placebo group (page 15, fourth paragraph, first sentence).

2.3.9 In this case there is no comparison with any treatment with risperidone, let alone with a sustained release form of risperidone, to show an improvement in efficacy related to the specific sustained release form with an osmotic dosage form and an ascending release rate over at least 8 hours. On that basis alone, an effect or advantage with respect to the dosage form of D8 cannot be shown by the Phase III Trial.

2.3.10 In addition, the facts that the dosage at 3 mg is equivalent to 1 mg immediate-response risperidone and that on that basis it should not be effective are mere assertions which are not proven by appropriate tests (see also point 2.3.5, above).

2.3.11 In view of that, an improvement in efficacy for the claimed dosage form with respect to the dosage forms of D8 cannot be acknowledged.

2.4 In the absence of effects or advantages supported by convincing experimental evidence, the problem solved can only be seen in the provision of a further dosage form for a drug which is therapeutically equivalent to that of D8.

3. The use of paliperidone as a therapeutic equivalent of risperidone has been accepted as well-known by both parties (see point 1.3, above). As to the specific dosage form, document D9 offers a very precise disclosure of an osmotic dosage form with ascending release rate over more than 8 hours which is suggested for use for a large number of medicaments.

3.1 Indeed D9 discloses devices which provide drug release at an ascending rate over an extended time period (page 1, lines 20 to 26). A preferred embodiment is a

tri-layer osmotic dosage form (page 21, lines 14 to 25 and figure 2) with a first drug layer (20), a second drug layer (18) with a higher drug concentration, a third push layer (28) containing an osmopolymer, a semipermeable membrane (56) surrounding the tri-layer tablet core to form a compartment and a suitable sized orifice (54). The ascending release rate can be maintained for a period of over 8 hours (e.g. about 16 hours in example 5, see page 34, lines 20 to 21) and several suitable drugs are mentioned including antipsychotics (page 8, line 18 to page 9, line 2, in particular page 8, line 28).

3.2 In any case, the fact that D9 discloses an osmotic dosage form with ascending release rate over more that 8 hours as according to claim 1, though not for paliperidone, was not disputed by the appellant-patent proprietor.

3.3 The skilled person looking for a further dosage form for a drug which is therapeutically equivalent to that of D8 would consider the replacement of risperidone with paliperidone in view of the acknowledged common general knowledge and the use of an osmotic dosage form with ascending release rate over more than 8 hours in view of the disclosure of D9. On that basis the skilled person would come to the subject-matter of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision without any inventive activity.

3.4 The dosage form of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision does not therefore involve an inventive step.

Auxiliary request – inventive step

4. The parties have provided, with regard to inventive step of the dosage form of claim 1 of the auxiliary request, no additional arguments with respect to the dosage form of claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision. The appellant-patent proprietor actually introduced the auxiliary request to react to objections of lack of sufficiency of disclosure and lack of clarity of the claims and not to the objection of lack of inventive step.

4.1 Indeed, as the dosage form disclosed in document D9 includes all the additional features of claim 1 of the auxiliary request (which has not been disputed by the appellant-patent proprietor, see also paragraphs 3.1 and 3.2, above), the dosage form of claim 1 of the auxiliary request does not involve an inventive step for the same reasons as detailed for claim 1 of the set of claims on which maintenance of the patent was based in the appealed decision (see points 1 to 3, above).

Conclusions

5. As both requests on file fail for lack of inventive step, there is no reason 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:

L. Fernández Gómez J. Riolo

Decision electronically authenticated