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Datasheet for the decision of 12 August 2010

Case Number: T 1253/06 - 3.3.02

Application Number: 98954933.2

Publication Number: 1019023

IPC: A61K 9/00

Language of the proceedings: EN

Title of invention:
Stabilized preparations for use in nebulizers

Patentee:
Nektar Therapeutics

Opponent:
Advanced Inhalation Research Inc

Headword:
Stabilized preparation/NEKTAR THERAPEUTICS

Relevant legal provisions:
EPC Art. 123(2), 54, 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Added matter - no: basis in the description as filed"
"Novelty - yes - undisclosed feature"
"Inventive steps - yes - non obvious alternative"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1253/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 12 August 2010

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 19 June 2006 rejecting the opposition filed against European patent No. 1019023 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 1 019 023, based on European application No. 98954933.2, was granted on the basis of 18 claims.

Independent claims 1, 9, 10 and 13 as granted read as follows:

1. A stable respiratory dispersion for use in a nebulizer comprising a fluorochemical continuous phase as a suspension medium having dispersed therein a plurality of perforated microstructures comprising at least one bioactive agent wherein said suspension medium substantially permeates said perforated microstructures.

9. A method for forming a stabilized respiratory dispersion according to any of claims 1 to 8, comprising the steps of:
combining a plurality of perforated microstructures comprising a least one bioactive agent with a predetermined volume of a non aqueous fluorochemical suspension medium to provide a respiratory blend wherein said suspension medium permeates said perforated microstructures and mixing said respiratory blend to provide a substantially homogeneous respiratory dispersion.

10. Use of a liquid fluorochemical in the manufacture of a medicament for the pulmonary delivery of a bioactive agent wherein the medicament comprises a stabilized dispersion according to any of claims 1 to 8 which is nebulized using a nebulizer to form an aerosolized medicament comprising said bioactive agent

wherein said aerosolized medicament is in a form for administration to at least a portion of the pulmonary air passages of a patient in need thereof.

13.A method for stabilizing a respiratory dispersion by reducing attractive van der Waals forces comprising the steps of:
providing a plurality of perforated microstructures;
combining the perforated microstructures with a fluorochemical suspension medium comprising at least one fluorochemical wherein the suspension medium substantially permeates the perforated microstructures and the medium and the microstructures are selected to provide a refractive index differential value of less than 0.5.

II. Opposition was filed against the patent under Article 100(a) EPC for lack of novelty, inventive step, exclusion from patentability and under Article 100(c) EPC because its subject-matter extended beyond the content of the application as filed.

The following documents *inter alia* were cited during the proceedings before the Opposition Division and/or the Board of Appeal:

(l) WO-A-96/26746
(2) WO-A-97/44013
(3) US-A-5611344
(4) WO-A-98/31346
(5) US-A-4620670.

III. By its decision pronounced on 5 May 2006, the Opposition Division rejected the opposition under Article 102(2) EPC.

In its decision, as to Article 100 (c) EPC, the Opposition Division expressed the view that the subject-matter of the contested claims 1 and 13 was disclosed in the application as filed.

Concerning novelty, the Opposition Division found that the feature relating to a dispersion comprising "a fluorochemical continuous phase as a suspension medium" rendered the subject-matter of independent claims 1, 9, 10 and 13 novel vis-à-vis the available prior art documents.

As regards inventive step, the Opposition Division was of the opinion that the combination of perforated microstructures with "a fluorochemical suspension medium" as an alternative to the known formulations in an aqueous medium was not derivable from any of the documents (1) to (4) taken alone or in combination, so that the subject-matter of independent claims 1, 9, 10 and 13 was inventive since they all contained this technical feature.

Concerning the interfering documents (2) and (4), the opposition division indicated in its decision that it did not investigate the priority right of the patent in suit since the claims were found to be novel and inventive over all cited documents, so that investigation of the priority right was not necessary.

It also indicated that the opponent withdrew its request for revocation on the basis of the ground of exclusion from patentability.

IV. The appellant (opponent) lodged an appeal against the said decision.

V. Oral proceedings were held on 12 August 2010.

The parties did not attend the oral proceedings.

VI. In its written submissions, the appellant disagreed with the favorable conclusions of the Opposition Division as to Article 123(2) EPC. It did not however indicate why the decision was not correct.

Concerning novelty, it mainly argued that documents (1) to (3) anticipated the subject-matter of the patent in suit.

As regards inventive step, it considered that the subject-matter of the patent in suit was rendered obvious by the combination of documents (3) and (5).

In its view, document (3), which was directed to the pulmonary delivery of active agent, represented the closest state of the art.

The problem to be solved vis-à-vis this document was to avoid the dissolution of the porous structures comprising the drug when using a water-based nebulisation system on water-soluble based formulations.

In its opinion, the solution to this problem consisting in employing a fluorochemical suspension medium as pharmaceutically acceptable and inert liquid phase that would not solubilise the drug product was obvious in the light of document (5), which shows that the use of inert propellants or dispersing media in pulmonary delivery was well known in the art.

Finally, it repeated its objections with respect to the priority right of the contested application.

VII. In its written submission, the respondent mainly agreed with the opposition division's favourable conclusions and analysis.

VIII. The appellant requested in writing that the decision under appeal be set aside and that the European patent be revoked.

The respondent requested in writing that the appeal be dismissed.

Reasons for the decision

1. The appeal is admissible.

2.1 Article 100 (c) EPC

The Board agrees with the Opposition Division’s favourable conclusions as to Article 100(c) EPC.

In fact, claim 1 and 13 find a basis in the application as originally filed on pages 9, lines 10 to 11 and 22

to 25, disclosing a liquid fluorochemical continuous phase, and in corresponding claims 28 and 21, which disclose the remaining features.

These claims read:

28. A stable respiratory dispersion for use in a nebulizer comprising a suspension medium having dispersed therein a plurality of perforated microstructures comprising at least one bioactive agent wherein said suspension medium substantially permeates said perforated microstructures.

21. A method for stabilizing a respiratory dispersion by reducing attractive van der Waals forces comprising the steps of:
providing a plurality of perforated microstructures;
combining the perforated microstructures with a suspension medium comprising at least one fluorochemical wherein the suspension medium and the perforated microstructures are selected to provide a refractive index differential value of less than about 0.5.

Having regard to the fact that the appellant neither put forward any new arguments compared with those submitted in writing and dealt with before the Opposition division nor indicated why the Opposition Division was wrong in that respect, there would appear to be no need to devote further attention to this issue.

Accordingly, the Board concludes that the subject-matter of the main request fulfils the requirements of

Article 100 (c) EPC (see Opposition Division's decision, page 6, point I).

2.2 Novelty

The Board agrees with the Opposition Division's favourable conclusions regarding Article 54 EPC.

Claim 1 reads:

1. A stable respiratory dispersion for use in a nebulizer
comprising a fluorochemical continuous phase as a suspension medium having dispersed, therein a plurality of perforated microstructures comprising at least one bioactive agent wherein said suspension medium substantially permeates said perforated microstructures

Thus, claim 1 of the patent-in-suit refers to a liquid, namely a fluorochemical continuous phase, in which the perforated microstructures are suspended.

Document (1) concerns a stabilised gas emulsion containing phospholipid for ultrasound contrast enhancement. The microspherical material of document (1) is exposed to at least a first gas, then dissolved in an aqueous liquid to form an aqueous gas emulsion composition.

This document describes the composition as comprising bubbles of the gas surrounded by a layer of the first and second surfactants (page 4, lines 11-13). The gas which permeates the particulate material may be a fluorocarbon (page 4, lines 22 and 24).

Document (1) states that fluorocarbons that are not gases at room temperature can be used provided that they have sufficient vapour pressure at body temperature and that it is important that the fluorocarbon does not condense at the partial pressure in the bubble or at body temperature (page 15, lines 22 to 33).

Thus, the teaching of this document is that, when present, the fluorocarbon is present in a gas form.

However, the relevant question for the assessment of novelty is whether the fluorocarbon forms the continuous phase of a suspension medium. According to page 5, line 9-13, document (1) relates to gas emulsions in which the discontinuous phase of the emulsion is the gas and it is clear from figure 1 that the particles are clearly not suspended in the gas medium.

In conclusion, document (1) does not disclose a suspension in which the microparticles are suspended in a fluorocarbon continuous phase.

Document (2) concerns aerodynamically light particles for pulmonary drug delivery.

According to page 16, lines 20-28, any biocompatible or pharmacologically acceptable gas, including fluorinated gases, can be incorporated into particles or trapped in the pores of particles.

This disclosure can neither be construed to mean that said gas forms the continuous phase of a suspension.

Indeed, this document also discloses that the particles may be administered alone or in a pharmaceutically acceptable carrier such as a liquid, for example saline (page 19, line 14-20). However, fluorochemicals are not disclosed in this context.

Document (3) discloses microencapsulated fluorinated gases for use as imaging agents.

The microcapsules have an outer polymer shell surrounding a core of gas (column 5, line 25-28).

It discloses that larger microcapsules/ microparticles may be administered by routes other than injection such as oral or inhalation (column 9, line 20-36). The capsules are however clearly filled by the fluorinated gas rather than being surrounded and suspended therein.

The appellant did not comment on Document (4).

For the sake of completeness, it is however noted that this document which relates to the preparation of particles for drug delivery to the pulmonary system contains no disclosure relating to a fluorochemical suspension medium.

Accordingly, the feature of a dispersion comprising a fluorochemical continuous phase as a suspension medium renders the subject-matter of claim 1 novel.

The same reasoning applies with respect to claims 9, 10 and 13 which all contain the novel feature "a fluorochemical suspension medium".

Accordingly, the Board concludes that the subject-matter of the main request fulfils the requirements of Article 54 EPC (see Opposition Division's decision, page 4 first paragraph, to pages 6 to 8, point II).

The Board cannot agree with the main appellant's argument in relation to novelty that a gas could form a "continuous phase" within the meaning of the claims, so that documents (1) to (3) would become relevant for the assessment of novelty.

It is indeed common general knowledge that in a suspension a solid is dispersed in a continuous phase being a liquid. In the present case the liquid is unambiguously a fluorochemical. This is moreover highlighted in the description of the patent in suit, where it is clearly required that the fluorochemical compound is in liquid form (paragraphs 19 and 20)

3. Inventive step

The Board agrees with the Opposition Division's favourable conclusions regarding Article 56 EPC.

3.1 The contested patent relates to a respiratory dispersion for use in a nebulizer, comprising a fluorochemical continuous phase as a suspension medium having dispersed therein a plurality of perforated microstructures comprising at least one bioactive

agent, wherein said suspension medium substantially permeates said perforated microstructures.

According to paragraph 6 of the patent in suit, standard formulations for nebulisation typically comprise aqueous-based solutions.

The Board agrees with the Opposition Division that this prior art, which concerns the same technical field as the patent in suit, represents the closest prior art.

3.2 The problem to be solved by the subject-matter of claim 1 of the patent in suit as against this prior art can be seen in the provision of a further stable dispersion for use in a nebuliser.

3.3. This problem is solved by using fluorochemicals as the suspension medium in the respiratory formulation as opposed to water based solutions.

In the light of the description and in particular examples XVIII and XX, which even indicates an improvement in the Deep Lung fraction values for dispersions of the patent in suit as compared to aqueous solutions, the Board is satisfied that the problem has been solved.

3.4 Thus the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

In that respect, the Board observes that, as it appears from the novelty analysis above under point 2., none of the documents (1) to (4) suggests this substitution.

There is indeed no single motivation for the skilled person in these documents to try fluorochemicals instead of water as a continuous phase of a formulation suitable for nebulisers.

Document (5), cited by the appellant with the grounds of appeal, is of no relevance either since it relates to the construction of nebulizers and does not mention suspensions.

Finally, the Board also agrees with the opposition division that, when a teaching is only found in the patent in suit, it is not permissible to use it in a problem-solution attack in the absence of a prior art document showing that it was indeed known to the skilled person. Thus the sentence in paragraph 3 of the patent in suit "... fluorochemical medium has also been explored", referred to by the appellant in its grounds of appeal, does prima facie not belong to the available prior art.

Accordingly, the skilled person would not identify fluorochemicals instead of water as a continuous phase of a formulation suitable for nebulisers as a possible alternative without inventive activity from the available prior art.

The same would apply when starting from document (3) as closest state of art, as proposed by the appellant.

In fact, this document is more remote from the subject-matter of claim 1 of the patent in suit. As this document does not even concern a suspension, the skilled person would have to perform a further step to

arrive at the subject-matter of claim 1 of the contested patent.

Accordingly, the subject-matter of independent claims 9, 10 and 13, as well as their dependent claims, which all contain the non-obvious feature relating to the use of fluorochemicals instead of water as a suspension medium, also involves an inventive step.

3.5 In the light of these facts, the Board can only conclude that the subject-matter of the set of claims as granted involves an inventive step as required by Article 56 EPC.

4. Priority

In its decision, the Opposition Division indicated that it did not investigate the priority right of the patent in suit since the claims were found to be novel and inventive over all cited documents, so that investigation of the priority right was not necessary.

As the Board arrived at the same conclusions as the Opposition Division, there appears to be indeed no need to investigate the priority right.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

N. Maslin U. Oswald