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Datasheet for the decision of 7 November 2006

Case Number: T 0256/03 - 3.3.02

Application Number: 95901923.3

Publication Number: 0735884

IPC: A61K 31/58

Language of the proceedings: EN

Title of invention:
Flunisolide aerosol formulations

Patentee:
MINNESOTA MINING AND MANUFACTURING COMPANY

Opponent:
Chiesi Farmaceutici S.p.A.

Headword:
Aerosol formulation/MINNESOTA MINING AND MANUFACTURING COMPANY

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - inventive step - yes: ex post facto analysis not permissible"

Decisions cited:
-

Catchword:
-

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Case Number: T 0256/03 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 7 November 2006

Appellant/opponent: Chiesi Farmaceutici S.p.A.
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 9 December 2002 concerning maintenance of the European patent No. 0735884 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 735 884, based on application No. 95 901 923.3, was granted on the basis of 20 claims.

Independent claims 1 and 17 as granted read as follows:

1. A solution aerosol formulation comprising: a therapeutically effective amount of flunisolide; a propellant comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2—tetrafluoroethane, 1,1,1,2,3,3,3— heptafluoropropane, and a mixture thereof; and ethanol in an amount effective to solubilize the flunisolide in the formulation.

17. A metered dose inhaler comprising: (i) an aerosol canister defining a formulation chamber; and (ii) a formulation according to Claim 1, wherein said formulation is contained within said formulation chamber.

II. Notice of opposition was filed against the granted patent by the appellant/opponent.

The patent was opposed under Article 100(a) EPC for lack of novelty and lack of inventive step.

The following document was *inter alia* cited during the proceedings.

(2) EP-A-372777

III. The interlocutory decision of the Opposition Division established that the patent could be maintained in an amended form under Article 106(3) EPC on the basis of

the text of auxiliary request 1 as submitted during the oral proceedings.

As to the main request(set of claims as granted), the Opposition Division considered that it was novel vis-à-vis document (2), because it was necessary to select the active compound flunisolide among a list of several other drugs, to select the compound ethanol among an other list of various compounds and further to select between a formulation in the form of a suspension or a solution to arrive at the subject-matter of claim 1 as granted.

However, the Opposition Division rejected the main request because its subject-matter was obvious vis-à-vis the disclosure in document (2).

The Opposition Division was of the opinion that, having regard to the beclomethasone solution formulations containing ethanol in examples 10 to 12 of document (2), the skilled person would replace the drug beclomethasone by the drug flunisolide in these formulations in order to obtain a solution aerosol formulation of that drug without inventive activity since document (2) mentioned both flunisolide and benclomethasone in the same list of medicaments which were envisaged in this document.

As to the first auxiliary request filed during the oral proceedings, the Opposition Division expressed the view that it did not contravene the requirements of Article 123(2) and (3) and of Article 84 EPC, since claim 1 was restricted to a formulation containing

0.005 per cent to 1 per cent by weight water as defined in claim 8 as originally filed and as granted.

Concerning novelty, the Opposition Division considered that this request was novel and noted that its novelty was, in fact, not contested.

As regards inventive step, the Opposition Division was of the opinion that the difference vis-à-vis the closest prior art document (2), namely the water ratio introduced in claim 1, was inventive since the claimed formulations containing water were more stable than those of the prior art and because the available prior art was silent on that.

IV. The appellant/opponent and the appellant/proprietor both lodged appeals against the said decision.

V. Oral proceedings were held before the Board on 7 November 2006.

VI. The submissions of the appellant/proprietor, in the written procedure and oral proceedings, can be summarised as follows:

It could not be predicted upon the basis of the disclosure of document (2) that flunisolide could be incorporated in a solution formulation because the teaching of this document was primarily directed at suspension formulations.

Moreover, although document (2) disclosed solution formulations of beclomethasone, it could not be predicted that flunisolide could be incorporated in a

solution formulation because, while they are both drugs are anti-inflammatory steroids, their physical properties were different, so the behaviour of one of the drugs in any formulation could not predicted on the basis of the behaviour of the other.

VII. The appellant/opponent mainly repeated the Opposition Division's arguments and conclusions as to inventive step in the written procedure and at the oral proceedings.

It emphasised that having regard to the chemical similarity between beclomethasone and flunisolide, the skilled person would have considered the replacement of beclomethasone by flunisolide in the solution formulations disclosed in examples 10 to 12 of document (2).

As to novelty, the appellant/opponent filed no new written submissions and it did not present any new arguments during the oral proceedings.

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

The appellant/proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or in the form upheld by the Opposition Division (first auxiliary request), or, as a second auxiliary request, on the basis of the set of claims filed by letter dated 13 August 2003.

Reasons for the decision

1. The appeals are admissible.

2. Main request

2.1 Novelty

The Board shares the analysis and positive conclusion of the Opposition Division as to novelty (point 2.1. of the Opposition Division's decision). In the absence of any arguments of the appellant/opponent as to why the Oppostion Division's decision does not hold good with respect to novelty, there is no need to develop this point further.

2.2 Inventive step

2.2.1 The patent provides for a solution aerosol formulation comprising a therapeutically effective amount of flunisolide, 1,1,1,2—tetrafluoroethane (HFC 134a) and ethanol in an amount effective to solubilize the flunisolide in the formulation (page 2, lines 40 to 43).

Document (2) discloses a a solution aerosol formulation comprising a therapeutically effective amount of beclomethasone, 1,1,1,2—tetrafluoroethane (HFC 134a) and a mixture of ethanol and surface active agent (surfactants) (see examples 10 to 12).

The parties and the Opposition Division have considered that document (2) represents the closest prior art.

The Board accepts this view.

2.2.2 According to the description of document (2), a compound of higher polarity than propellant 134a such as ethanol, pentane, isopentane or neopentane must be added in the formulation in order to increase the solubility of the surfactant in the propellant. This document, which concerns formulation both in the form of a solution (3 examples) and in the form of a suspension (51 examples), teaches also that "large amounts of solubilised surfactant may also assist in obtaining stable solution formulations of certain drugs" (page 3, lines 13 to 17, together with page 4, lines 41 to 45; claim 2). Numerous drugs are mentioned on page 5, lines 12 to 23, among which are flunisolide and beclomethasone.

Having regard to the patent in suit (page 3, lines 11 to 13; page 2, lines 6 to 10), flunisolide is dissolved in ethanol, so that the aerosol formulation is in the form of a solution which avoids the drawbacks of a formulation in the form of a suspension such as crystal polymorphism, and moreover enables the use of any soluble polymorphic form of flunisolide in preparing the formulation.

Accordingly, the problem to be solved as against document (2) can be seen as the provision of a flunisolide formulation in the form of a solution wherein the flunisolide is dissolved without using surfactants.

2.2.3 This problem is solved by the subject-matter of claim 1, namely by the use of ethanol as solvent, and, in the light of working examples of the description of the

patent in suit (see eg examples 1 and 2), the Board is satisfied that the problem has been solved.

This, moreover, has not been contested by the appellant/opponent.

2.2.4 Thus, the question to be answered is whether the proposed solution, ie the use of ethanol as a solvent to dissolve the drug flunisolide, was obvious to the skilled person in the light of the prior art.

In that respect, the Board notes that document (2) is silent about the use of ethanol as a solvent for the various drugs mentioned on page 5, lines 12 to 24. In fact, the document teaches that it is the presence of large amounts of solubilised surfactant in the formulations which might assist in obtaining solution formulations of certain unspecified drugs. In that respect, ethanol is only disclosed as an ingredient used to dissolve increased amounts of surfactants in the propellant (page 3, lines 13 to 17, together with page 4, lines 41 to 45).

The Board observes also that this document is both concerned with formulations both in the form of a suspension and in the form of a solution.

Moreover, having regard to the fact that the only information alone relating to the solubility of flunisolide would not have prompted the skilled person towards the use of a polar protic solvent such as ethanol to dissolve flunisolide, since, as agreed by the parties, flunisolide was known to be insoluble in water and only slightly soluble in methanol, ie protic

polar solvents, the Board is therefore satisfied that the solution to the problem stated under point 2.2.3 could not be derived in an obvious way from the available prior art.

2.2.5 The main argument raised by the appellant/opponent was that the skilled person would have replaced beclomethasone by flunisolide in the examples of document (2) without inventive skill, because flunisolide was also mentioned as a suitable drug in document (2) and because they both belong to the family of anti-inflammatory steroids.

2.2.6 The Board cannot share the opinion of the appellant/opponent.

The Board agrees that the skilled person could have replaced beclomethasone by flunisolide in the examples of document (2) without inventive skill, by merely following the teaching of said document.

This, however, is not the question to be answered for the assessment of inventive step in the present case.

The question is whether the skilled person would have done this with the expectation that it would then get a formulation in the form of a solution rather than a suspension and that he could dispense with surfactants in the formulation.

For the reasons given under point 2.2.4, the Board remains convinced that the skilled person would not have done this in the light of the available information.

In fact, the skilled person had no reason to believe that the replacement of beclomethasone by flunisolide in the examples of document (2) would also lead to a solution rather than a suspension and that surfactants could be dispense with in the formulation, in particular because surfactants are disclosed as mandatory ingredients of the formulations in document (2).

The reasoning of the appellant/opponent appears therefore to be based on an *ex post facto* analysis.

Moreover, the appellant/opponent's argument that ethanol is an usual ingredient in aerosol formulations does not *per se* constitute an incentive to try, since, as mentioned under point 2.2.4, the known information concerning the solubility of flunisolide in polar protic solvent would have discouraged the skilled person from using it as a solvent for flunisolide.

Indeed, the appellant opponent did not contest the information provided by the appellant proprietor that flunisolide was known to be only "slightly soluble in methanol" whereas beclomethasone was known to be "freely soluble" in alcohol.

As the same considerations apply to the second alternative of claim 1, the Board considers, in view of the foregoing, that the subject-matter of claim 1 of the set of claims as granted involves an inventive step as required by Article 56 EPC.

Since claim 1 is allowable, there is no need for the Board to consider the remaining independent claim, since it refers to the subject-matter of claim 1 .

Under these circumstances, there is also no need to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar The Chairman

A. Townend U. Oswald