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Datasheet for the decision of 14 September 2021

Case Number: T 1306/18 - 3.3.07

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Language of the proceedings: EN

Title of invention:
INHALATION COMPOSITION CONTAINING ACLIDINIUM FOR TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patent Proprietor:
Almirall, S.A.

Opponents:
Hexal AG
Generics (U.K.) Limited

Headword:
Aclidinium for the treatment of COPD / ALMIRALL

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - main request (yes)
Inventive step - main request (yes) - reasonable expectation of success (no)

Decisions cited:
T 1409/06

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Case Number: T 1306/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 September 2021

Appellant: (Patent Proprietor)	Almirall, S.A. Ronda del General Mitre 151 08022 Barcelona (ES)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent: (Opponent 1)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Opponent 2)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 March 2018 revoking European patent No. 2265257 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	K. Kerber-Zubrzycka

Summary of Facts and Submissions

I. European patent 2 265 257 (hereinafter "the patent") was granted on the basis of 18 claims. Claim 1 of the patent read as follows:

"A pharmaceutical composition comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable dry powder carrier, providing a metered nominal dose of aclidinium equivalent to 400 µg (plus/ minus 10%) aclidinium bromide for use by inhalation in the treatment of chronic obstructive pulmonary disease."

II. Two oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

III. The opposition division took the decision to revoke the patent.

The decision was based on a main request and auxiliary requests 1-11 filed on 20 December 2016 (respectively as auxiliary requests 4, 7-14 and 18-20) and auxiliary requests 12-16 filed on 28 November 2017 (as auxiliary requests 21-25).

Claim 1 of the main request was identical to claim 1 as granted (see I. above).

IV. In the decision of the opposition division, reference was made in particular to the following documents:

D1: G.F. Joos et al., "Bronchodilator effects on aclidinium bromide, a novel long-acting anticholinergic, in COPD patients: a Phase II study". Abstract presented at the Annual Congress of the European Respiratory Society (ERS) in Stockholm, Sweden. September 16, 2007. Abstract 1299.
D2: G.F. Joos et al., "Bronchodilator effects on aclidinium bromide, a novel long-acting anticholinergic, in COPD patients: a Phase II study". Poster presented at the Annual Congress of the European Respiratory Society (ERS) in Stockholm, Sweden. September 16, 2007. E-Poster 1299.
D3: Printout of the European Respiratory Society (ERS) webpage relating to the presentation of D1 and D2, September 16, 2007, pages 209s-210s
D5: WO 2005/115466 A
D38: 2006 Guidelines issued by the Global Initiative for Chronic Obstructive Lung Disease
D42: D. Singh et al., Pulmonary Pharmacology & Therapeutics 25, 248-253 (2012)
D43: E.M. Kerwin et al., COPD 9, 90-101 (2012)
D44: P.W. Jones et al., Eur. Respir. J. 40, 830-836 (2012)

V. In particular, the opposition division decided that:

(a) The main request met the requirements of Rule 80 EPC and of Articles 123(2) and (3) EPC. Its subject-matter was sufficiently disclosed and novel over D5.

D1/D2 and D3 were equivalent starting points for the assessment of inventive step, and each

disclosed the use of aclidinium for the treatment of chronic obstructive pulmonary disease (COPD). Starting from the embodiment of D1/D2 comprising 300 µg aclidinium bromide, the subject-matter of the main request differed in the metered nominal dose of aclidinium equivalent to 400 µg (plus/minus 10%) aclidinium bromide.

This difference did not result in any improved therapeutic effect. An absence of any increase in side effects could not be taken into account because it could not be deduced from the patent. The objective technical problem was to provide an alternative composition for the treatment of COPD. Since D2 concluded that aclidinium was safe and well tolerated at all tested dosages including 900 µg, the skilled person had no reason to expect that adverse effect would appear when increasing the dosage from 300 to 400 µg. Even if the absence of increase in side effects was taken into account (based on D42-D44), the claimed subject-matter did not involve an inventive step in light of D2.

Thus the main request did not fulfill the criteria of inventive step.

(b) The subject-matter of claim 1 of each of auxiliary requests 1-16 also lacked an inventive step.

VI. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division.

With its statement setting out the grounds of appeal, the appellant filed a main request and auxiliary requests 1-16. The main request was identical to the main request underlying the appealed decision, i.e.

claim 1 of the main request was identical to claim 1 as granted (see I. above).

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA issued on 25 May 2021.

VIII. Oral proceedings were held before the Board, by videoconference, on 14 September 2021.

IX. The appellant's arguments can be summarised as follows:

(a) Novelty

The subject-matter of claim 1 of the main request resulted from multiple selections within D5, in particular the selection of COPD, the selection of the dose of 400 µg, and the selection of the route of administration. Since D5 did not contain any pointer to this combination, the subject-matter of the main request was novel over D5.

(b) Inventive step

The invention related to aclidinium bromide for use in the treatment of COPD. At the priority date of the patent, aclidinium was known to be a long-acting anticholinergic drug ("LAMA"). LAMAs were only used in the treatment of COPD for maintenance therapy (i.e. given regularly on a long term basis to reduce symptoms), and not as rescue medication (i.e. to provide rapid effective relief for an acute COPD exacerbation). A clinician devising an appropriate LAMA dosage for long term chronic use would have selected the minimum dose possible to achieve the desired clinical effect, because the toxicity arising from

bronchodilator drugs was generally known to be dose related.

The closest prior art D1 or D2 reported a preliminary phase IIa trial based on a single administration of aclidinium to each patient, using two plausible investigational doses (100 µg and 300 µg), together which a much higher dose (900 µg) which the skilled reader would have understood not to be intended as a dose likely to be used in clinical practice.

D1 and D2 taught that a maximum effect was achieved at 300 µg, thus suggesting a dose between 100 µg and 300 µg for practical therapeutic administration rather than a dose in excess of 300 µg. Furthermore, a skilled clinician reading D1 and D2 could not have concluded that there would be no change in the side effect profile seen following acute dosing of aclidinium bromide when the drug was administered over the medium or long term when increasing the dosage from 300 µg to 400 µg. In contrast, the patent reported a clinical trial in which 460 patients had been administered the drug every day for 4 weeks, thus modelling the chronic maintenance therapy in which LAMAs such as aclidinium were in practice used (see paragraphs [0043] and [0044] of the patent).

For these reasons, the claimed dose was a non-obvious alternative to the dosages suggested in D1 and D2.

X. The arguments of opponent 1 (respondent 1) and opponent 2 (respondent 2) can be summarised as follows

(a) Novelty

D5 disclosed a range of 50 µg to 400 µg (see page 29, paragraph 3; see also the range of 2-400 µg on page 23, lines 1-5) of an M3 antagonist which, preferably, was aclidinium bromide (see paragraph bridging pages 32 and 33; page 8, last paragraph). Thus, D5 directly and unambiguously disclosed aclidinium bromide at a dose of 400 µg. D5 further disclosed the treatment of asthma or COPD (see claims 1 and 2, page 23-29). Thus the subject-matter of claim 1 of the main request lacked novelty over D5.

(b) Inventive step

D1/D2 represented the closest prior art. D1/D2 addressed the problem of safe and effective treatment of COPD, and disclosed a dry powder inhalation composition comprising a single metered nominal dose of aclidinium (100 µg, 300 µg or 900 µg) for the treatment of COPD. The starting point within D1/D2 was the 300 µg dosage, which provided a better bronchodilatory effect than 100 µg and was well tolerated from a safety perspective.

The subject-matter of the claims differed from D1/D2 by the metered nominal dose of aclidinium equivalent to 400 µg aclidinium bromide.

No improvement in tolerability achieved with the dose of 400 µg could be taken into account, because this technical effect was not demonstrated by comparison with the 300 µg embodiment of the closest prior art, and because it was neither implied by nor related to the technical problem initially suggested in the originally filed application. Hence, no technical

effect was associated with the distinguishing feature. The objective technical problem was the provision of an alternative composition for the treatment of COPD.

Since D1/D2 disclosed that both 300 µg and 900 µg were effective and safe, a value between these two limits, such as 400 µg, would have been expected to have the same satisfactory efficacy and safety profile. The mere determination of the dosage regimen which provided the optimum effect by routine optimisation did not involve an inventive step (T 1409/06, point 3.2.1 of the reasons).

Contrary to the appellant's view, D1 and D2 were not limited to acute interventions. This is because Dl and D2 related to "COPD" and "COPD patients", and hence would be considered as valuable sources of information concerning the treatment of chronic obstructive pulmonary disease. Furthermore, the claims of the main request did not require multiple dosing as an essential feature. Lastly, no indication that a technical effect was associated with this feature over the prior art was discernible from the patent.

Hence the subject-matter of the main request did not involve an inventive step.

XI. The appellant requests that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, or, alternatively, on the basis of one of auxiliary requests 1-16, all filed with the grounds of appeal.

XII. Both respondent 1 and respondent 2 request that the appeal be dismissed.

Reasons for the Decision

The present decision is based on the appellant's main request, filed with the grounds of appeal and identical to the main request underlying the appealed decision.

1. Added subject-matter and sufficiency of disclosure

The opposition division found that the main request complied with the criteria of sufficiency of disclosure and of Article 123(2) EPC.

In its statement setting out the grounds of appeal (see pages 3 and 4), under the headings "Added matter under Art. 100(c), 123(2) EPC" and "Insufficient disclosure under Art. 100(b), 83 EPC", respondent 1 merely states that reference is made to the written submissions in first instance, without addressing the reasons in the decision under appeal. Thus respondent 1 did not substantiate why the appealed decision should be set aside in these respects.

Accordingly, the Board sees no reasons to depart from the conclusions of the opposition division in this matter. The main request meets the requirements of sufficiency of disclosure and of Article 123(2) EPC.

2. Novelty over D5

D5 discloses (see claims 1, 7, 11) a combination of a corticosteroid and an antagonist of M3 muscarinic receptors for the treatment of inflammatory or obstructive diseases of the respiratory tract such as asthma or COPD. Aclidinium bromide is the most preferred M3 muscarinic receptor antagonist (see the

paragraph bridging pages 32 and 33 and all the examples). The composition is preferably in unit dosage form, for example a tablet, capsule or metered aerosol dose (see second paragraph on page 29). Each dosage unit contains 20-1000 µg, preferably 50-400 µg of an M3 antagonist (see third paragraph on page 29). D5 also generally considers an administration by inhalation, with doses of "between 2µg and 400 µg of each therapeutically active ingredient" (see page 23, lines 1-5; second paragraph on page 30).

However D5 contains no pointer to the combination of a metered dose of 400 µg aclidinium bromide and of the treatment of COPD. The subject-matter of claim 1 of the main request results from selections both in respect of the condition to be treated (asthma of COPD) and the dose of aclidinium bromide.

Accordingly, for this reason at least, novelty over D5 is established.

3. Inventive step

3.1 The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications.

Each of D1 (abstract 1299) and D2 relate to the treatment of COPD with aclidinium bromide by administration of a single dose of 100, 300, and 900 µg using a dry powder inhaler (DPI). The opposition division chose the embodiment of D1/D2 with a dosage of 300 µg as closest prior art, because this value is

closer to the claimed dosage of 400 µg, and in view of its stronger bronchodilatory effect observed in D2 (see Table 2). The Board concurs.

3.2 The subject-matter of claim 1 of the main request differs in the metered nominal dose of aclidinium equivalent to 400 µg (plus/minus 10%) aclidinium bromide.

3.3 According to the appellant, this claimed metered nominal dose leads, in the context of long term maintenance therapy, to an improved efficacy without increase in side effect.

3.3.1 Regarding the alleged improved efficacy, the Board is not convinced by the evidence on which the appellant relies (namely D42-D44), because these comparative data only compares the claimed dose of 400 µg with doses of 100 or 200 µg. No evidence of any improvement in efficacy over the dose of 300 µg of the closest prior art is offered.

3.3.2 However, the same post-published evidence credibly shows that the claimed dose of 400 µg allows for an effective long term treatment of COPD without increase in side effects.

In particular, both D43 and D44 show, in phase III studies, that twice-daily aclidinium 400 µg was not only effective in the maintenance treatment of COPD but also well tolerated and did not lead to any increase in adverse effects, as compared with the dose of 200 µg. D44 concludes that "Aclidinium 200 µg and 400 µg b.i.d for 24 weeks was well tolerated, with no differences between the safety profiles of the two doses" (see D44, page 835, right column, lines 18-20; see also D43, page

99, right column, penultimate paragraph: "Both doses were well tolerated and had similar safety profiles").

Considering that the toxicity of bronchodilators is generally dose related (see D38, page 51, right hand column), the Board accepts the appellant's argument that, if the doses of 200 and 400 µg do not differ in safety profile, no difference between the dose of 300 µg of the closest prior art and the claimed dose of 400 µg is to be expected.

3.4 According to the respondents, the technical effects alleged by the appellant, in particular the absence of increase in toxicity, are not to be taken into account for the assessment of inventive step. The Board does not share this opinion for the following reasons.

3.4.1 Firstly, the distinction made by the appellant, in the treatment of COPD, between rescue medication and long term maintenance therapy is supported by D38 (see page 51, lines 1-5, left hand column) and is not contested. Rescue medication refers to the provision of a rapid and effective relief for an acute COPD exacerbation, whereas long term maintenance therapy is given regularly on a long term basis to reduce symptoms.

The respondents point out that the wording of claim 1 of the main request is not limited to a use in long term maintenance therapy, but also covers rescue therapy. The respondents do not, however, contest that aclidinium is known to be a long-acting anticholinergic drug ("LAMA"), which is used only in the treatment of COPD for maintenance therapy (see the introduction of D2, fourth point). Accordingly, the Board considers that the effect on safety profile in maintenance therapy can be taken into account.

3.4.2 The respondents also criticise the absence of data regarding safety profile for the dose of 400 µg in the application as filed.

However, the Board concurs with the appellant that these effects are sufficiently connected to the technical problem mentioned in the application as filed to justify a reformulation of the objective technical problem for the purposes of inventive step. The clinical data reported in the application as filed (see example 1) involve a once-daily treatment with, among others, a dose of 400 µg aclidinium for 4 weeks. The suitability of the claimed aclidinium dose in long-term maintenance therapy is thus sufficiently shown in the application as filed. Furthermore, at the end of the clinical study of example 1, it is observed that "Aclidinium was well tolerated, with no dose-dependent effect on ECG, laboratory parameters or adverse events" (paragraph [0043] of the application as filed) and that the 400 µg dose was selected as the investigational dose for long term clinical trials on the basis of not only efficacy but also tolerability data (paragraph [0044] of the applicationas filed). Accordingly, the clinical data of D42-D44 merely confirm the teaching of the application as filed and can be taken into account in the assessment of inventive step.

3.5 Consequently, the technical problem starting from D1 or D2 is to provide an aclidinium composition for the safe and effective treatment of COPD.

3.6 In the Board's opinion, the skilled person starting from D1 and D2 could not anticipate, with a reasonable expectation of success, that the claimed dose of 400 µg

would allow an effective treatment of COPD in long term maintenance therapy without excessive toxicity. Even if the clinical studies reported in D1 and D2 are aimed at finding an appropriate dosage regimen for the treatment of COPD, the data reported therein are limited to single administrations of each of the studied doses. Therefore, irrespective of whether D1 and D2 show stable or increasing efficacy or toxicity for the single administration of 100, 300 or 900 µg aclidinium, these preliminary studies do not permit to draw any conclusion as to the safety profile of the dose of 400 µg aclidinium in a long term therapy. In these circumstances, the choice of the dosage regimen of 400 µg cannot be regarded as resulting from routine experimentations, because the fact that doses above 300 µg have acceptable toxicity profiles in maintenance therapy is not obvious starting from D1 or D2. The skilled person could not have arrived at this conclusion with reasonable certainty without the clinical data of the patent, completed by D42-D44. Thus, the present case differs from T 1409/06 in which the board considered the requirements of inventive step not to be met because the effect arising from the selection of a specific unit dose was "already known or obvious" (see T 1409/06, point 3.2.1 of the reasons).

Accordingly, the subject-matter of the main request involves an inventive step.

Order

For these reasons it is decided that:

1. The appealed decision is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the main request filed with the grounds of appeal and a description to be adapted thereto.

The Registrar: The Chairman:

L. Malécot-Grob A. Usuelli

Decision electronically authenticated