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**Datasheet for the decision
of 6 May 2008**

Case Number: T 1028/05 - 3.3.02

Application Number: 98944373.4

Publication Number: 1014993

IPC: A61K 31/57

Language of the proceedings: EN

Title of invention:

New Use for Budesonide and Formoterol

Patentee:

AstraZeneca AB

Opponents:

Chiesi Farmaceutici S.p.A.
NORTON HEALTHCARE LTD
Generics[UK] Limited

Headword:

New therapeutic use/ASTRAZENECA AB

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main, first, second requests - inventive step - no: obvious combination"

Decisions cited:

T 0009/81, T 0936/96

Catchword:

-



Case Number: T 1028/05 - 3.3.02.

DECISION
of the Technical Board of Appeal
of 6 May 2008

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Party as of right

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Decision under appeal:

Decision of the Opposition Division of the European Patent Office posted 21 June 2005 rejecting the opposition filed against European patent No. 1014993 pursuant to Article 102(2) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

- I. European patent No. 1 014 993, based on European application No. 98 944 373.4, was granted on the basis of 10 claims.

Independent claims 1 and 3 as granted read as follows:

1. Use of a composition comprising, in admixture or separately:
 - (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
 - (b) a second active ingredient which is budesonide; and a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1, in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

3. Use of a kit containing:
 - (i) a vessel containing a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
 - (ii) a vessel containing a second active ingredient which is budesonide;
 - (iii) a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1; and
 - (iv) instructions for the simultaneous, sequential or separate administration of the first and second active ingredients to a patient in need thereof; in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

- II. Oppositions were filed by opponents O1, O2 and O3 against the patent under Article 100(a) EPC for lack of novelty and inventive step and Article 100(b) EPC for insufficiency of disclosure.

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

(1) WO 9311773

(14) IMS (A) Data in Switzerland; (B) Foreword of Schweizer Diagnosen Index (SDI), IMS, Institut für Medizinische Information und Statistik, Gartenstr. 2, 6300 Zug, Switzerland; (C) Letter of IHA IMS health dated May 7, 1999; (D) Basic Reference Manual, Vol. 1, Revised Edition 1988, issued by IMS International.

(18) Trechsel K., Foradil in medical practice: seven case study, Ciba Geigy, 1992.

(21) Cazzola, M. et al. Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease, Pulmonary Pharmacology 7, 103-107, (1994).

(25) Nederlands tijdschrift voor geneeskunde, 1996, 13 January, 140(2)

(26) English translation of page 95 of (25).

(44) Roberts S.J. et al. Thorax 49(11): 1090-1095(1994).

III. By its decision pronounced on 11 May 2005, the Opposition Division rejected the oppositions under Article 102(2) EPC (1973).

As to Article 100(b), the Opposition Division considered that the objection of insufficiency of disclosure was not founded.

The objection to claim 1 that in a composition the two ingredients could not be "separate" was regarded as a clarity objection, and the objection to claim 3 was not followed either, because the "kit of parts" decision (T 009/81), allowed such a claim.

Concerning novelty, the Opposition Division was of the opinion that the "prior use" according to documents (14) did not anticipate claim 1, because "simultaneous prescription" did not imply the joint use of formoterol and budesonide in a form of a kit of parts.

Document (1) was also considered as not being novelty-destroying, because it did not disclose the treatment of COPD (Chronic Obstructive Pulmonary Disease).

Nor were documents (25/26) and (18) regarded as novelty-destroying, because they did not unambiguously disclose that formoterol and budesonide were used together.

As regards inventive step, the Opposition Division defined the problem to be solved over the closest prior art document (21), which disclosed the use of formoterol in the treatment of COPD, as the provision of an improved treatment of COPD such that the exacerbations in COPD can be reduced.

In the view of the Opposition Division, the solution of this problem, i.e. the combination of formoterol with

budesonide, was inventive, because the effect of the reduction of exacerbations obtained by combining budesonide with formoterol was not predictable in the light of the available prior art.

- IV. The appellants (opponents O2 and O3) lodged an appeal against the said decision.
- V. Oral proceedings were held before the Board on 6 May 2008.
- VI. During the oral proceedings, the appellants held essentially that, in view of the fact that document (1) disclosed that the combination of formoterol and budesonide might be used to treat respiratory disorders such as asthma, the problem to be solved was the identification of other respiratory disorders that might be treated using the combination.

The skilled person, reading this document, would have looked to identify which other respiratory disorders might be treated with the combination of the long acting β 2-agonist formoterol and the corticosteroid budesonide.

To do this, the skilled person would reasonably have referred to document (44). On page 1092, the data in Table I shows that anti-asthma drugs, including inhaled bronchodilators and inhaled steroids, alone or together (listed as "Steroid+ bronchodilator" under Inhalers" in Table I and discussed in the first sentence under the heading "Results" on the same page), were prescribed to patients with asthma, COPD and bronchitis. Of the 1605 patients diagnosed with COPD, 727 (equivalent to 45.3%)

were prescribed both an inhaled steroid and an inhaled bronchodilator.

As explained on page 1091, first column, second paragraph, the prescribed bronchodilator included β 2-agonist, and the inhaled steroids were beclomethasone or budesonide.

The appellants indicated that there was no reference in document (44) to formoterol, the reason for this being that formoterol was not available in the United Kingdom during the period covered by the study.

Therefore, on reading document (1), the skilled person, aware of the teaching in document (44) and intent upon solving the above-identified technical problem at the priority date of the patent in suit, would immediately have used the combination of formoterol and budesonide to treat patients suffering from COPD and thereby would have arrived at the subject-matter claimed in the patent in suit.

The appellants also referred to several scientific studies to show that budesonide was useful in the treatment of COPD.

In their written submissions, the appellants also developed further combinations of prior art documents to demonstrate the absence of inventive step for the claimed subject-matter and raised a novelty objection vis-à-vis document (1) and vis-à-vis an alleged prior use in Switzerland.

The objection relating to Article 100(b) EPC was not maintained during the appeal proceedings.

VII. The respondent (patent proprietor) submitted two auxiliary requests with its letter dated 29 February 2008.

Claim 1 of auxiliary request 1 reads:

1. Use of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
(b) a second active ingredient which is budesonide; and
a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1, in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

Claim 1 of auxiliary request 2 reads:

1. Use of a composition comprising, in admixture:
(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
(b) a second active ingredient which is budesonide; and
(c) one or more pharmaceutically acceptable additives, diluents and/or carriers and a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1, in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

During the oral proceedings the respondent's main line of argument in reply to the inventive step objection vis-à-vis the combination of document (1) with document (44) relied on the fact that the skilled person - defined by the respondent as a post-doctoral medical student who was an expert in the field of COPD - would not pay attention to document (44) because it is merely concerned with the prescribing trends for anti-asthmatic drugs in the UK, without any evidence on the efficacy of the treatments.

The respondent also referred to several scientific studies to show that the benefit of using a corticosteroids such as budesonide in the treatment of COPD was not demonstrated.

The respondent concluded that the claimed subject-matter was therefore inventive, the more so having regard to the unexpected reduction in exacerbations and/or better sleep and synergism achieved by the combination.

In its written submissions, the respondent shared the Opposition Division's favourable conclusions as to novelty vis-à-vis document (1) and the alleged prior use.

VIII. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed (main request), or that the patent be maintained in amended form on the basis of one of the first and

second auxiliary requests filed with letter of 29 February 2008.

Reasons for the decision

1. The appeal is admissible.
2. Main request (patent as granted)
 - 2.1 Article 100(b) EPC

The appellants did not maintain the objection raised during the opposition procedure with respect to Article 100(b) EPC, and the Board sees no reason to disagree with the favourable conclusions of the Opposition Division in that respect (see above under III, and the Opposition Division's decision, point I).

Moreover, having regard to the Board's conclusions in the assessment of inventive step (see below, point 2.3.6), there would appear to be no need to devote further attention to this issue.

- 2.2 Novelty vis-à-vis document (1)

The Board agrees with the Opposition Division's favourable conclusions regarding novelty vis-à-vis document (1), because this latter does not disclose COPD.

Having regard to the Board's conclusions in the assessment of inventive step (see below, point 2.3.6) and to the fact that the appellant did not put forward new arguments compared with those submitted and dealt with before the Opposition Division, there would appear

to be no need to devote further attention to these issues.

Accordingly, the Board concludes that the subject-matter of the main request fulfils the requirements of Article 123 EPC (see above under III, and the Opposition Division's decision, item b)).

2.3 Inventive step

- 2.3.1 The contested patent is concerned with the use of the combination comprising the bronchodilator formoterol with the corticosteroid budesonide for the treatment of chronic obstructive pulmonary disease (column 1, lines 5 to 8).

Document (1) entitled "New combination of formoterol and budesonide" recites in the first paragraph, page 1: "This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma and to pharmaceutical compositions containing the two active ingredients."

As indicated during the oral proceedings, the Board considers that this document, which discloses the use of the identical combination for the treatment of respiratory disorders such as asthma, represents the closest prior art, since, as will appear from the following, it offers the most promising springboard towards the invention.

2.3.2 The problem to be solved by the subject-matter of claim 1 of the main request of the patent in suit as against document (1) can only be seen in the identification of other respiratory disorders that may be treated using the known combination.

2.3.3 This problem is solved by identifying COPD as another respiratory disorder to be treated with the known combination comprising the bronchodilator formoterol with the corticosteroid budesonide.

In the light of the description and examples in the patent in suit, and in the absence of any specific evidence to the contrary, the Board is satisfied that the problem has been solved.

2.3.4 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.

Document (44), published only three years before the priority date of the contested patent, appears to be highly relevant in that respect.

This document is a survey of prescribing habits for inhaled anti-asthmatic drugs in the UK in the 1992/3. Anonymised patient-specific prescription and diagnostic data were extracted from computerised general practice records for the Northern region of the UK (total population 330 749) whose data had been validated for inclusion in a research database. Patients were included if they were either prescribed an inhaled steroid or bronchodilator during a 12-month period, or had a recorded diagnosis of asthma, bronchitis or chronic obstructive pulmonary disease.

On page 1092, Table 1, the document discloses the number and percentage of patients prescribed anti-asthma drugs and alternative treatment for those with respiratory diagnoses in the study population of 330 749 registered patients. For each patient issued a prescription for inhaled steroids (beclomethasone, budesonide) or bronchodilators (salbutamol, terbutaline, fenoterol, salmeterol), drug-based data detailed the number of prescriptions issued during the year, the daily dose of the first prescription, and all recorded indications for the prescription.

For patients with a recorded diagnosis of asthma, bronchitis or COPD, the data included both the diagnosis and information on all respiratory medicines prescribed (if any). The COPD was carefully screened to exclude patients with symptoms compatible with asthma.

Table 1 shows that about half those diagnosed with COPD (no asthma) were treated with inhalers (751) and that some 40% of these patients (727) were treated with both a steroid and a bronchodilator.

Thus, the Board observes that, from this table, it is apparent that the prescription of both steroids and bronchodilators for the treatment of COPD was widespread in the UK in 1992/3.

Under these circumstances, the Board is convinced that the skilled person aware of document (44) would have had every motivation to try the formulation of document (1) in the treatment of COPD.

2.3.5 The Board does not agree with the respondent's argument that the skilled person, defined as a post-doctoral medical student, expert in the field of COPD, would not pay attention to document (44) because it is merely concerned with the prescribing trends for anti-asthmatic drugs in the UK, without any scientific evidence on the efficacy of the treatments.

The figures in document (44) clearly show that there was a strong opinion in the field of COPD that the combination of steroids and bronchodilators was an efficient treatment for COPD (the contested patent merely demonstrates that this opinion was not wrong).

The Board is convinced that the skilled person, also when defined as a post-doctoral medical student, expert in the field of COPD, would pay attention to a widespread opinion.

On the contrary, the skilled person would certainly not be deterred from trying the existing medication for COPD in the light of a few documents which put into question the efficacy of budenoside, since, as discussed during the oral proceedings, the studies in these documents concerned an very limited number of patients (8 to 35) over a very short period of time (4 to 12 weeks), which were moreover contradicted by other studies.

As to the unexpected effects, the Board considers that the present situation is similar to that in T 936/96 cited by the appellants (see points 2.6 and 2.7), i.e. that once a realistic technical problem had been defined and once it had been established that a

particular solution to such a problem would have been envisaged by a skilled person in the light of the relevant state of the art, that solution cannot be said to involve an inventive step (see above 2.3.1 to 2.3.4), and the claimed surprising effects inherent to the alleged invention cannot be regarded as an indication of the presence of an inventive step which could alter the previous findings of obviousness.

In conclusion, the Opposition Division was wrong in deciding that the subject-matter was inventive merely because of the effect of the reduction of exacerbations.

- 2.3.6 In the light of these facts, the Board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step as required by Article 56 EPC.

Under these circumstances, there is no need to consider the remaining claims. There is also no need to consider the other objections relating to lack of novelty, in particular vis-à-vis the alleged prior use in Switzerland and the other inventive step attacks.

3. Auxiliary requests 1 and 2

During the oral proceedings, all parties agreed that the auxiliary requests did not add anything new in relation to the assessment of inventive step, and therefore merely referred again to their submissions with respect to the main request.

Thus, as there are no additional distinguishing features in these requests vis-à-vis the combination of

documents (1) and (44), the conclusion as to lack of inventive step for the subject-matter of claim 1 of the main request applies equally to the auxiliary requests.

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

N. Maslin

U. Oswald