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# Datasheet for the decision of 28 October 2014

**Case Number:** T 0383/10 - 3.3.01

**Application Number:** 00902663.4

**Publication Number:** 1158970

**IPC:** A61K31/135, A61K31/46, A61P11/00

**Language of the proceedings:** EN

**Title of invention:**
COMBINATIONS OF FORMOTEROL AND A TIOTROPIUM SALT

**Patent Proprietors:**
Novartis AG
Novartis Pharma GmbH

**Opponent:**
NORTON HEALTHCARE LIMITED

**Headword:**

**Relevant legal provisions:**
RPBA Art. 13
EPC 1973 Art. 56

**Keyword:**
Admission of late-filed request (yes)
All requests: inventive step (no) - obvious solution

**Decisions cited:**

**Catchword:**

Europäisches Patentamt
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**Beschwerdekammern**
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**Case Number: T 0383/10 - 3.3.01**

# D E C I S I O N
## of Technical Board of Appeal 3.3.01
## of 28 October 2014

| | |
|---|---|
| **Appellant:** (Opponent) | NORTON HEALTHCARE LIMITED<br>Regent House<br>5-7 Broadhurst Gardens<br>Swiss Cottage<br>London NW6 3RZ (GB) |
| **Representative:** | Gillard, Richard Edward<br>Elkington and Fife LLP<br>Thavies Inn House<br>3-4 Holborn Circus<br>London EC1N 2HA (GB) |
| **Respondents:** (Patent Proprietors) | Novartis AG<br>Lichtstrasse 35<br>4056 Basel (CH)<br><br>Novartis Pharma GmbH<br>Brunner Strasse 59<br>1230 Wien (AT) |
| **Representative:** | Warner, James Alexander<br>Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 14 December 2009 rejecting the opposition filed against European patent No. 1158970 pursuant to Article 101(2) EPC.** |

**Composition of the Board:**

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|---|---|
| **Chairman** | A. Lindner |
| **Members:** | G. Seufert |
| | T. Karamanli |

## Summary of Facts and Submissions

I. The appellant (opponent) lodged an appeal against the decision of the opposition division rejecting the opposition against European patent No. 1 158 970.

II. Independent claim 1 of the patent as granted reads as follows:

"1. A medicament containing (A) formoterol fumarate dihydrate and (B) tiotropium bromide as a combined preparation for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease."

Hereinafter formoterol fumarate dihydrate is also referred to as "formoterol" and tiotropium bromide as "tiotropium".

III. In this decision the following numbering will be used to refer to the documents

(5) D. Faulds *et al.*, Drugs, Vol. 42, No. 1, 1991, pages 115 to 137
(7) F. P. V. Maesen *et al.*, Eur. Respir. J., Vol. 8, 1995, pages 1506 to 1513
(10) P. J. Barnes, TiPS, Vol. 19, 1998, pages 415 to 423
(14) CA 2 280 099
(15) SCRIP No. 1552, 1990, page 26
(18) WO 00/69468
(24) Foradil, Product information, 1993, pages 1 to 50
(25) The Role of Anticholinergics in Chronic Obstructive Pulmonary Disease and Chronic Asthma, Edited by P. J. Barnes and A. S. Buist,

1998, Chapt. 8 and 9, pages 126 to 144

(32) Asthma Therapy, P. J. Barnes, S. Godfrey, 1998, Martin Dunitz Ltd. (UK), pages 90 to 135

(35) "Statement of Professor Neil Christopher Barnes", dated 29 November 2011, submitted by the appellant with letter of 7 December 2011

(36) D. P. Tashkin, G. T. Ferguson, Respiratory Research, Vol. 14, No. 49, 2013, pages 1 to 13

(39) Extract from Chiesi 2010 Annual Report, page 20

IV. Notice of opposition was filed requesting revocation of the patent in suit in its entirety on the grounds of lack of inventive step (Article 100(a) EPC).

V. In the contested decision, the opposition division held that the subject-matter of the claims as granted involved an inventive step starting from document (24) as the closest state of the art, taking into consideration the unexpected synergistic effects and the decreased cardiac side-effect of the claimed combination.

VI. In its statement of grounds of appeal, the appellant maintained its objection of lack of inventive step.

VII. In its reply to the statement of grounds of appeal, the respondents (patent proprietors) defended the patent in suit on the basis of the claims as granted.

VIII. With letter of 7 December 2011, the appellant filed further documents, including document (35).

IX. In a communication accompanying the summons to oral proceedings the board expressed its preliminary opinion with respect to inventive step.

X. Under cover of a letter dated 28 August 2014, the respondents filed further documents, including documents (36) and (39), and auxiliary request 1. Claim 1 of auxiliary request 1 reads as follows:

"1. A medicament containing (A) formoterol fumarate dihydrate and (B) tiotropium bromide as a combined preparation for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease, wherein the inflammatory or obstructive airways disease is COPD."

At the oral proceedings before the board, the respondents filed auxiliary request 2, with claim 1 reading as follows:

"1. A medicament containing (A) formoterol fumarate dihydrate and (B) tiotropium bromide as a combined preparation for simultaneous administration in the treatment of an inflammatory or obstructive airways disease, wherein the medicament is a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier."

One of the issues discussed in detail during the oral proceedings was the mismatch of duration of action of the active ingredients and the question whether this constituted a deterrent or prejudice which would have prevented the skilled person from combining these ingredients, in particular in a mixture for simultaneous administration.

XI. The arguments of the appellant with regard to the decisive issues can be summarised as follows:

- Admission of auxiliary request 2

Auxiliary request 2 was late-filed and should not be admitted into the proceedings. The respondents introduced the issue concerning the mismatch of duration of action. They should have been aware that their arguments were not valid for the claimed separate administration and should thus have filed this request at an earlier stage of the appeal proceedings.

- Inventive step

Document (24), which was directed to a long-acting, well tolerated $\beta_2$-agonist with a rapid onset of action in the treatment of asthma and chronic obstructive pulmonary disease (COPD), was a suitable starting point for the assessment of inventive step. The only effect that has been credibly demonstrated was the improved bronchodilator efficacy. Thus, the problem to be solved was the provision of a medicament with improved bronchodilator efficacy compared to each component alone. With regard to the decreased cardiac side-effects, document (18) did not show any unexpected effects. Furthermore, a synergistic effect between formoterol and tiotropium allowed the use of lower individual doses. A further decrease in cardiac side-effects, for which $\beta_2$-agonists were known, was therefore predictable. The proposed solution was obvious in view of document (25), which provided a clear rationale for the combination of a $\beta_2$-agonist and an anticholinergic agent, namely an expected improvement in efficacy. Said document also mentioned tiotropium as suitable anticholinergic agent. It was long-acting and selective for certain subreceptors, which offered potential clinical advantages over non-selective anticholinergic

agents. The use of a $\beta_2$-agonist, such as formoterol and salmeterol, in combination with an anticholinergic agent was also known from document (32) in the treatment of asthma. The fact that other avenues for further developing an improved medicament were also open to the skilled person was not relevant and could not render inventive an approach which was otherwise obvious to try.

The arguments with respect to auxiliary request 1 were basically the same. The results of salmeterol in combination with tiotropium were not relevant. Furthermore, the mismatch in duration of action was not relevant, since, as discussed in the context of the main request, claim 1 of auxiliary request 1 was not limited to fixed dose combinations. It was furthermore apparent from document (25) that the duration of action was dose-dependent. Moreover, the presently claimed combination did not solve the problem concerning the mismatch of duration of action. It simply tolerated this disadvantage. The appellant's expert was aware of the difference in the duration of action. He could not be relied on as evidence that the skilled person would not consider combining formoterol and tiotropium.

The subject-matter of the second auxiliary request did not involve an inventive step. For the skilled person the use of both ingredients in a single mixture was merely a matter of trade-off between the known advantages of better compliance when using a single mixture and the known disadvantages of having less control over the optimum dose. Furthermore, merely tolerating the disadvantages was not a sign of inventive step. Moreover, the skilled person was taught in document (25) that the duration of action was dose-dependent. No inventive skills were required in finding

an acceptable compromise for a simultaneous administration for a combination that was obvious to try.

XII. The arguments of the respondents with regard to the decisive issues can be summarised as follows:

- Admission of auxiliary request 2

Auxiliary request 2 was filed in response to the objection concerning the mismatch of action and the separate administration, which was raised for the first time in the oral proceedings before the board. The issue of mismatch of duration of action was raised by the appellant in connection with document (35), not by the respondents. Furthermore, the amendments were straightforward and did not raise new issues.

- Inventive step

Document (24) was a suitable starting point for the assessment of inventive step. In the light of said document the problem to be solved was the provision of a medicament with improved, in particular synergistic, therapeutic benefits, and minimal side-effects, in particular a reduction in cardiac side-effects. Documents (18) and (36) provided evidence that these effects were in fact achieved. The combination of formoterol and tiotropium was not obvious without the benefit of hindsight. The skilled person had numerous options for further developments, as confirmed by documents (35) and (10). In the absence of any indication in documents (24) or (25) as to a combination with tiotropium and in the absence of any known combination of a long-acting $\beta_2$-agonist and a long-acting anticholonergic agent, on which the skilled

person could base any expectation of the benefits, the presently claimed combination was not obvious. Document (25) referred to short-acting $\beta_2$-agonist. Moreover, it recommended ipatropium as the ideal anticholinergic agent. Tiotropium was a drug which was still under investigation and required further research with regard to therapeutic potential and tolerability. This would have discouraged the skilled person from its use. Furthermore, the mismatch of duration of action between formoterol and tiotropium provided the skilled person with a clear pointer against the combination of these two compounds, in particular in view of the fact that the skilled person at the time of the invention had compounds at his disposal with a better match of duration of action, such as salmeterol or carmoterol. It was also a surprising result that the combination of these more promising candidates turned out to be inferior to the presently claimed combination. A match of duration of action was essential. Otherwise, complex administration schemes were required, which increased the patients' risks for getting it wrong and in addition reduced patient compliance.

Concerning auxiliary request 1, the skilled person had two options for the $\beta_2$-agonist at the time the invention was made. The choice of formoterol was not arbitrary taking into account that the claimed combination turned out to be much better than the combination with the alternative $\beta_2$-agonists.

The mismatch of duration of action was a particularly clear deterrent for the skilled person to use formoterol and tiotropium in a mixture for simultaneous administration as claimed in auxiliary request 2, which could easily lead to the over- or underdosing of one of the components. Although it was true that the duration

of action of tiotropium could be modulated to a certain extent, such a modulation entailed the risk that at low doses tiotropium had no action.

XIII. The appellant requested that the decision under appeal be set aside and that the European patent be revoked in its entirety.

XIV. The respondents requested that the appeal be dismissed or, as an auxiliary measure, that the patent be maintained on the basis of the claims according to auxiliary request 1 filed with letter dated 28 August 2014 or auxiliary request 2 filed during oral proceedings on 28 October 2014.

XV. At the end of the oral proceedings the decision of the board was announced.

## Reasons for the Decision

1. The appeal is admissible.

*Main request*

2. Inventive step

2.1 Claim 1 as granted is directed to a medicament containing formoterol, a $\beta_2$-agonist, and tiotropium, an anticholinergic agent, for the treatment of inflammatory or obstructive airways diseases. The diseases include asthma and COPD.

2.2 The use of $\beta_2$-agonists or anticholinergic agents in the treatment of inflammatory or obstructive airways diseases is well known in the art. Equally disclosed in

the prior art is the use of either formoterol or tiotropium alone in the treatment of airway diseases (documents (24), (5), (7) or (10)). This is also acknowledged in the patent in suit (paragraph [0002]).

In the decision under appeal, the opposition division considered document (24) as the closest state of the art. This document is directed to a medicament comprising formoterol as active agent in the treatment of asthma and COPD (page 8, last paragraph; page 10; page 43, last paragraph). The medicament is well tolerated, long acting and has a rapid onset of effects (page 3, first two paragraphs and last paragraph). Side-effects are infrequent and typical for $\beta_2$-agonists (page 3).

The board sees no compelling reasons to deviate from the opposition division's choice of the closest state of the art and, in accordance with both parties, takes document (24) as a suitable starting point for the assessment of inventive step.

2.3 In the light of document (24), the respondents, at the oral proceedings before the board, formulated the problem to be solved as the provision of a medicament with improved, in particular synergistic, therapeutic benefits, and minimal side-effects (see also paragraph [0004] of the patent in suit).

The proposed solution according to the respondents was the combination of formoterol with tiotropium.

In support of the asserted effects, the respondents relied on document (18) (page 12, lines 25 to 29 and 34 to 36, Figs. 1 and 2, in particular Figure 1) and

document (36) (page 4, left-hand column, Chap. "Free combinations of LAMA plus LABA"; page 5, table 3).

2.4 It was undisputed between the parties that documents (18) and (36) demonstrated improved/ synergistic bronchodilator efficacy of the claimed combination compared to that of each of the compounds alone.

Concerning the alleged minimisation of side-effects, in particular cardiac side-effects, the board notes that according to the patent in suit this minimisation is merely the consequence of the improved or synergistic effect of the combination, since it provides **the possibility** of lowering the individual dosages compared with those of each of the components alone for a given therapeutic (bronchodilator) effect (see paragraph [0004]). This is particularly important with respect to the $\beta_2$-agonist (i.e. formoterol), since $\beta_2$-agonists are known for their undesirable cardiac side-effects. These effects are dose-dependent and particularly pronounced at high doses. The board concurs with the appellant that nothing beyond these known and expected effects has been shown in document (18), which is the only document that is concerned with the cardiac side-effects. In view of the above, the board sees no reason to consider the minimisation of side-effects, in particular cardiac side-effects, as a genuinely separate effect.

The board also notes that claim 1 as granted is not limited to a particular dose for each of the individual components and encompasses also combinations with a high dose of formoterol with the inevitable occurrence of cardiac side-effects.

It follows from the above that the problem to be solved in the light of document (24) is seen in the provision of a medicament with improved/synergistic bronchodilator efficacy.

2.5 In view of the evidence provided by the respondents, this problem has been plausibly solved by the combination of formoterol and tiotropium. This was also conceded by the appellant.

2.6 It remains to be decided whether the proposed solution is obvious in view of the available prior art.

The person skilled in the art has a comprehensive knowledge in the field of treating inflammatory and obstructive airway diseases. He is thus aware of document (25), a textbook on the treatment of COPD and chronic asthma. This document suggests the combination of a $\beta_2$-agonist and an anticholineric agent in the treatment of COPD (see Chapter 9 entitled "Anticholinergics and $\beta_2$-agonists: Efficacy, safety and combination therapy in chronic obstructive pulmonary disease"; in particular page 141, last complete paragraph). The rationale behind the combination is enhanced efficacy (i. e. an expected additive/ synergistic effect; see page 142, lines 9 to 11 and Table 1, point 1) with no additional side-effects and possibly improved patient compliance. Moreover, in the same Chapter 9, on page 138 of document (25), several anticholinergic agents are mentioned, such as ipatropium bromide, oxitropium bromide and the recently developed long-acting tiotropium. In this context, explicit reference is made to Chapter 8 of the same textbook. In said chapter, entitled "Tiotropium bromide: A new long-acting anticholinergic bronchodilator", the existence of several muscarinic

(cholinergic) receptor sub-types ($M_1$ to $M_5$) and their function is described. The skilled person is taught that tiotropium is selective for the $M_1$- and $M_3$-, but not the $M_2$-subreceptor. By avoiding the blockade of the $M_2$-subreceptor, which is suspected counteracting the bronchodilator response and accounting for the cases of paradoxical bronchoconstriction, it may therefore offer clinical advantages over the conventional non-selective anticholinergic agents, like ipatropium or oxitropium bromide (see page 129, third and fourth paragraphs; page 134, lines 3 to 10)). Thus, document (25) not only provides the skilled person with a clear pointer to combine a $\beta_2$-agonist and an anticholinergic agent with the expectation of improving the efficacy, but also provides a clear incentive for the use of tiotropium as a long-acting, more selective and therefore potentially more advantageous anticholinergic agent. The claimed subject-matter is therefore obvious in the light of document (24) in combination with the disclosure in document (25). The same suggestion to combine a $\beta_2$-agonist, such as salmeterol or formoterol, and an anticholinergic agent, such as ipatropium or oxitropium bromide, in the treatment of asthma can also be found in document (32), a further textbook (see page 102, left-hand column, "Step 4").

2.7 According to the respondents, the skilled person starting from document (24) and faced with the technical problem of providing a medicament with improved efficacy had a number of choices on how to proceed. This was even conceded by the appellant's expert, who, in document (35), referred to several options available to the skilled person, such as a combination of a long acting $\beta_2$-agonist with a steroid for the treatment of COPD in addition to asthma, a

combination of formoterol with a steroid for rescue relief of asthma in addition to maintenance therapy or the combination of a long-acting $\beta_2$-agonist with an anticholinergic (see document (35), paragraphs 10, 11 and 12). The fact that numerous options for further developments were available to the skilled person was also confirmed by document (10). The skilled person was therefore not in a one-way street leading him - without the benefit of hindsight - directly to the claimed combination. Furthermore, the respondents argued that there was no disclosure or suggestion in document (24) to use formoterol in combination with other therapeutic agents, let alone tiotropium bromide. Neither was the combination of a long-acting $\beta_2$-agonist and a long-acting anticholinergic agent known in the prior art, on which the skilled person could base any expectation of benefits. Document (25) was concerned with short-acting agonists and anticholinergic agents (page 137, first paragraph, lines 7 to 10)). Furthermore, said document recommended the use of ipatropium bromide as an ideal agent for treatment of COPD and asthma (page 127, first paragraph; page 139, last paragraph). According to the respondents, tiotropium was still very much an investigational drug. Only a limited amount of data on its clinical effect was published (page 132, second and fourth paragraphs) and further studies were needed to assess its therapeutic potential and tolerability profile. Hence, the skilled person would be discouraged from using tiotropium. In Chapter 9, document (25) merely theorised on potential benefits. It also indicated that the patients often showed subjective improvement with combination therapy in contrast to either agent alone, which would discourage the skilled person from using such combination therapy. The respondents also pointed out that it was not yet established whether selective anticholinergic agents

actually had the alleged advantages over existing non-selective anticholinergic agents (document (10), page 416, left-hand column below "Box 1", lines 2 to 4).

2.8 Concerning the respondents' arguments on the various options available to the skilled person when starting from document (24), the board notes that, in the present case, the question is not only whether the skilled person starting from this document is provided with enough information that he could have arrived at the claimed solution, but whether he would find in the prior art incentives motivating him to modify the disclosure of the closest state of the art in a way leading to the claimed invention in expectation of the improvement he was searching for. For the reason set out in point 2.6 above, the board is convinced that this is the case here. The clinical data available on the tiotropium may be small, as pointed out by the respondents, but they demonstrate that it is an effective and well-tolerated anticholinergic agent. No serious adverse effects were reported (document (25), page 132, third paragraph). Furthermore, there is also a clear indication that due to its selectivity tiotropium may offer additional advantages over the non-selective anticholinergics. Even if, as stated on page 134, lines 3 to 10 of document (25), there is a need for long-term studies to assess the full therapeutic potential and tolerability profile, this in the board's conviction cannot be interpreted as discouragement or prejudice against using tiotropium.

Nor is the respondents' argument convincing that the skilled person would not consider using tiotropium because it was not yet established whether selective anticholinergic agents actually have the asserted

advantage to avoid the occasionally observed paradoxical bronchoconstriction. The board notes that in order to render a solution obvious it is not necessary for the skilled person to be able to predict all advantages with certainty. It is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success. In the present case, document (25) provides the skilled person with a clear rationale for combining a $\beta_2$-agonist and an anticholinergic agent, namely the expected enhanced efficacy. It also provides a clear incentive for the use of tiotropium as anticholinergic agents, namely its long duration of action and high selectivity. The board therefore sees no reason why the skilled person would not have contemplated combining tiotropium with the well-known long-acting $\beta_2$-agonist formoterol in order to solve the technical problem as formulated in point 2.4 above.

The absence of any reference with regard to tiotropium in document (24) is not relevant in the present context. Such a reference would be equal to a novelty-destroying disclosure. However, a novelty-destroying document is not a prerequisite for successfully attacking inventive step.

Concerning the respondents' argument that the teaching of document (25) was restricted to short-acting $\beta_2$-agonists, the board notes that such a teaching is not apparent from document (25). In the clinical rationale for combining $\beta_2$-agonist and anticholinergics no distinction is made between various bronchodilators or anticholinergic agents. It is true that due to the presence of "somewhat more comprehensive data", chapter 9 of document (25) focuses more on short-acting

$\beta_2$-agonists, but this cannot be equated with a prejudice against the use of long-acting $\beta_2$-agonists, such as formoterol. The fact that no such prejudice existed is also confirmed by document (32) referring to the combined use of long-acting $\beta_2$-agonists and anticholinergics in the treatment of asthma or document (15) suggesting the same.

2.9 Finally, the respondents argued that the skilled person would not have considered combining formoterol and tiotropium in view of a clear mismatch of their duration of action. The latter was 12 hours for formoterol (document (24), page 3, first line) and 24 or 32 hours, respectively for tiotropium (document (25), page 132, last paragraph; document (10), page 416, left-hand column below figure, lines 12 to 14). A match in duration of action was necessary for an effective combination product. Mismatch in duration of actions entailed the risk of overdosing or underdosing the individual components. In support for their arguments, the respondents relied on the statement of the appellant's expert, Professor Barnes, in particular on paragraphs 26, 27 and 29 of document (35).

2.10 The board does not agree. The respondents misconstrue the observation and comments of Professor Barnes, which have been made in a particular context. In the paragraphs referred to by the respondents, Professor Barnes comments on the teaching of document (14) and the recommendations a clinician would have made for further developments had he been referred to that particular document (see document (35), page 6, section entitled "The 099 Application" including paragraph 23 to 27; page 2, paragraph 4). However, document (14) is not the closest prior art, since it is concerned with a

specific pressure-liquefied propellent mixture. Moreover, Professor Barnes discusses the difference in duration of action in the context of a twice-daily maintenance treatment, for which the short-acting anticholinergic oxitropium mentioned in document (14) is not suitable (document (35), paragraph 26, in particular last two lines). In the subsequent paragraph, Professor Barnes continues with the statement that a clinician would have advised replacing the short-acting oxitropium with tiotropium. Since Professor Barnes was undoubtedly aware of the duration of action of formoterol and tiotropium, the board cannot follow the respondents' interpretation that according to Professor Barnes a technical prejudice exists which would deter the person skilled in the art from using active ingredients with differences in their duration of action.

The board also notes that present claim 1 allows for separate administration of each individual component, for which a match in duration of action has no technical significance. Each component can be taken according to needs. In the present case, it is perfectly feasible to have a twice-daily administration of formoterol (as known from document (24)) and a separate once-daily dose of the long-acting tiotropium (as suggested in document (25); page 133, penultimate paragraph), without requiring complicated administration schemes, which could affect patient compliance, or leading to serious risks of over- or underdosing, as argued by the respondents.

The board is therefore convinced that the alleged mismatch in duration of action is not a sufficient reason for the skilled person to disregard the combined

use of tiotropium and formoterol in the treatment of airway diseases.

In view of the above, the board also does not accept the respondents' argument that the presently claimed medicament was not obvious, because at the priority date the skilled person, with respect to matching duration of action, had more suitable candidates than formoterol at his disposal, such as salmeterol having a five times longer duration of action than formoterol, or carmoterol having a 30-hour duration of action. A match in the duration of action is not particularly relevant, if the components are administered separately. Furthermore, the choice of using an allegedly less advantageous $\beta_2$-agonist does not require inventive ingenuity, if, as in the present case, it merely amounts to tolerating a clearly predictable disadvantage. Furthermore, the fact that more than 10 years after the priority date of the patent in suit salmeterol and carmoterol allegedly turned out to be inferior to the claimed combination, due to a non-competitive profile of carmoterol (document (39)) or still inconclusive benefits of a combination of salmeterol and tiotropium (document (36), page 4, left-hand column, last paragraph, lines 1 to 2 and right-hand column, lines 12 to 14) is of no relevance, in this context, since it could not have influenced the skilled person's choice of $\beta_2$-agonist at the time the invention was made.

2.11 For the reasons set out above, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC 1973, with the consequence that the main request must be refused.

*Auxiliary request 1*

3. Inventive step

3.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the inflammatory or obstructive disease is limited to COPD. In view of the fact that both documents (24) and (25) include the treatment of COPD (see points 2.2 and 2.6 above), this limitation does not affect the assessment of inventive step as set out in point 2 above. Hence, the same considerations and conclusion as set out above for the main request still apply to auxiliary request 1.

3.2 According to the respondents, the limitation to COPD affected the assessment of inventive step. In this context, they relied again on the statement of Professor Barnes, in particular paragraphs 29 and 30 of document (35). The respondents argued that, according to Professor Barnes, the skilled person when developing a medicament for COPD had two equivalent options for the $\beta_2$-agonist, namely salmeterol and formoterol. As could be seen from document (36) (page 4, left-hand column, last paragraph, first two lines and right-hand column, lines 12 to 14), the data regarding improvements with salmeterol and tiotropium were inconclusive. The use of formoterol in combination with tiotropium was thus not an arbitrary choice, but turned out to provide much better results.

3.3 The board does not agree. Firstly, the observation of Professor Barnes are made with regard to document (15) as the starting point for further developing a product for the treatment of asthma and COPD. With document (24) as the starting point, the question whether to use salmeterol or formoterol does not arise.

Furthermore, in view of the fact that the skilled person did not know at the time the invention was made how a combination with salmeterol and tiotropium would eventually turn out, he could not have made a purposive choice by selecting formoterol. Formoterol and salmeterol were both suitable candidates for the skilled person at the time the invention was made.

3.4 Furthermore, the respondents stressed again the clear mismatch of duration of action of formoterol and tiotropium, which would prevent the skilled person from using them in combination. In particular, they pointed out that such a mismatch made the administration significantly more complex, could seriously undermine patient compliance and significantly increased the risks for patients of getting the administration wrong, which could easily lead to over- or underdosing.

3.5 For the same reasons as set out in point 2.10 above, the board does not agree with the respondents. Like claim 1 of the main request, claim 1 of auxiliary request 1 provides for a separate administration for which a match of duration of action is not relevant. Furthermore, none of the difficulties mentioned by the respondents are overcome for the presently claimed separate administration.

3.6 In view of the above, the board concludes that the subject-matter of claim 1 of auxiliary request 1 does not involve an inventive step within the meaning of Article 56 EPC 1973, with the consequence that auxiliary request 1 must also be refused for lack of inventive step.

*Auxiliary request 2*

4. Admission

4.1 Auxiliary request 2 was filed at the oral proceedings before the board. It is an amendment to the respondents' case within the meaning of Article 13(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the admission of which is at the board's discretion. In exercising due discretion, it is established jurisprudence of the boards of appeal to consider *inter alia* the complexity of the amendments, the current state of the proceedings and the need for procedural economy. Amendments that require the postponement of the oral proceedings are not admitted (Article 13(3) RPBA).

4.2 The appellant objected to the admission of this request since it was late-filed (see point XI above).

4.3 The board notes that auxiliary request 2 was filed in direct response to the preceding discussion, in an attempt to address the board's objections regarding the mismatch in the duration of action and the separate administration, an issue which arose for the first time in the discussion that took place at the oral proceedings before the board. Furthermore, the amendment in claim 1 was a straightforward limitation to a simultaneous administration by including the feature of dependent claim 2 of the main request. This neither increased the complexity of the case nor did it give rise to fresh issues which the board or the appellant could not reasonably expect to deal with without adjourning the oral proceedings. This was not contested by the appellant.

4.4 Hence, the board decided to admit auxiliary request 2 into the proceedings.

5. Inventive step

5.1 Claim 1 of auxiliary request 2 is directed to a medicament for simultaneous administration comprising formoterol and tiotropium in a mixture.

5.2 According to the respondents, the mismatch in duration of action would clearly teach away from the currently claimed fixed dose combination. In this context, the respondents relied again on the statement of Professor Barnes, according to whom a mismatch in duration of action was a sufficient reason for not combining formoterol and oxitropium (paragraph 26 of document (35)). In the respondents' opinion, the same reasoning should apply for a mixture of formoterol and tiotropium. In addition, the use of a fixed dose combination would have the advantage of being more convenient for the patients and therefore improve patient compliance.

5.3 As set out in point 2.10 above, the board does not agree with the respondents' interpretation of Professor Barnes' comments, which were made in a particular context, namely the suitability of a combination of a short-acting anticholineric agent and a long-acting $\beta_2$-agonist in a twice-daily maintenance treatment. Hence, Professor Barnes' observations cannot be used to establish a general technical prejudice against the combination of active ingredients whose duration of action do not match.

Furthermore, the skilled person is undoubtedly aware of the fact that fixed dose combinations are more

convenient for patients and may therefore result in an improvement of patient compliance. However, he is also aware of the fact that such fixed dose combinations provide less control with respect to the optimum dose for the individual active ingredient. The board therefore cannot follow the respondents' contention that the skilled person would have been dissuaded from using formoterol and tiotropium in a fixed dose combination. On the contrary, the board concurs with the appellant that the skilled person would consider this as a matter of trade-off between the expected advantages (convenience and patient compliance) and disadvantages (less control over the optimum dose).

Moreover, in the present case, the skilled person is taught in document (25) that the bronchodilator activity is dose-dependent. Over a range of 10 to 160 µg, it persisted for 10 to 15 hours in most patients (see page 132, third paragraph, lines 4 to 7). This provides the skilled person with a certain flexibility to adapt the dose of tiotropium in such a way as to reach an acceptable compromise with the duration of action of the $\beta_2$-agonist. It should also be noted that, in the present case, the skilled person would be aware of the fact that this flexibility is further increased due to the expected enhanced efficacy, which permits further reduction in the individual doses below those known for individual components.

The respondents' argument that the skilled person would have been deterred from using formoterol with tiotropium in a mixture for simultaneous administration cannot therefore succeed.

5.4 For the reasons set out above, the board concludes that the subject-matter of claim 1 of auxiliary request 2 does not involve an inventive step within the meaning of Article 56 EPC 1973. Accordingly, this request must be refused.

## 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:

M. Schalow A. Lindner

Decision electronically authenticated