

Internal distribution code:

- (A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

**Datasheet for the decision
of 18 October 2018**

Case Number: T 0259/14 - 3.3.01

Application Number: 04741123.6

Publication Number: 1651224

IPC: A61K31/4704, A61K31/46,
A61K31/137, A61K31/439,
A61P11/06

Language of the proceedings: EN

Title of invention:

MEDICAMENTS FOR INHALATION COMPRISING AN ANTICHOLINERGIC AND A
BETAMIMETIC

Patent Proprietor:

Boehringer Ingelheim International GmbH
Boehringer Ingelheim Pharma GmbH & Co. KG

Opponent:

Teva UK Limited

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - (no)



Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0259/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 18 October 2018

Appellant: Teva UK Limited
(Opponent) Field House
Station Approach
Harlow
Essex CM20 2FB (GB)

Representative: Gillard, Richard Edward
Elkington and Fife LLP
Thavies Inn House
3-4 Holborn Circus
London EC1N 2HA (GB)

Respondent: Boehringer Ingelheim International GmbH
(Patent Proprietor 1) Binger Strasse 173
55216 Ingelheim am Rhein (DE)

Respondent: Boehringer Ingelheim Pharma GmbH & Co. KG
(Patent Proprietor 2) Binger Strasse 173
55216 Ingelheim am Rhein (DE)

Representative: Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 2 December 2013
rejecting the opposition filed against European
patent No. 1651224 pursuant to Article 101(2)
EPC.**

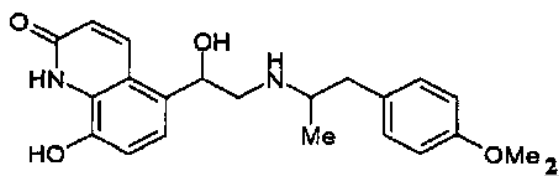
Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
 P. de Heij

Summary of Facts and Submissions

- I. European patent No. 1 651 224 was granted with a set of twenty claims. Independent claim 1 reads as follows:

"1. Pharmaceutical compositions, comprising one or more, preferably one anticholinergic 1 and a betamimetic of formula 2



optionally in the form of its diastereomers, mixtures of its diastereomers [sic], racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof and optionally together with a pharmaceutically acceptable excipient, wherein the anticholinergic 1 is a tiotropium salt."

- II. The compound according to formula 2 is also known as carmoterol (INN) or TA-2005.
- III. A notice of opposition was filed in which revocation of the patent was requested under Article 100(a) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step and extended beyond the content of the application as filed.
- IV. The documents cited in the opposition and appeal proceedings included the following:
- D1: EP 1 157 689 A1
D5: EP 0 147 719 A2

D14: Pulmonary Pharmacology & Therapeutics 20, 250-257
(2007)

D15: Current Opinion in Pharmacology 3, 270-276
(June 2003)

D17: Gen. Pharmac. 27(4), 575-580 (1996)

D20: Biol. Pharm. Bull. 17(8) 1047-1052 (1994)

- V. The decision under appeal is the decision of the opposition division announced on 11 October 2013 and posted on 2 December 2013 rejecting the opposition.
- VI. According to the decision under appeal, the subject-matter of the claims as granted did not go beyond the content of the application as filed and was novel over the disclosure of document D1. Document D15, which represented the closest prior art, disclosed the possible combined use of tiotropium bromide and long-acting β_2 -adrenoreceptor agonists (LABAs) to treat lung diseases, naming formoterol and salmeterol as possible LABAs. Claim 1 as granted was directed to the combination of tiotropium with carmoterol. The objective technical problem was the provision of improved combinations. Document D15 did not contain any pointer identifying carmoterol as a possible combination partner for tiotropium. The data provided in post-published document D14 showed that the claimed combination provided a therapeutic benefit which was unexpectedly superior to that of the combinations envisaged in D15. It was therefore acknowledged that the claimed subject-matter involved an inventive step.
- VII. The opponent (appellant) filed an appeal against this decision.
- VIII. The patent proprietors (respondents) requested the dismissal of the appeal and, with their reply (dated

29 July 2014) to the statement setting out the grounds of appeal, submitted an amended set of claims as their auxiliary request.

Claim 1 of the auxiliary request is identical to claim 1 of the patent as granted (i.e. of the main request), except that the term "*tiotropium salt*" was replaced by "*tiotropium bromide*".

IX. Oral proceedings before the board were held on 18 October 2018.

X. The appellant's arguments may be summarised as follows:

Inventive step - main request

The compositions according to claim 1 as granted differed from the combinations envisaged in document D15 in the choice of carmoterol as the LABA compound which was to be combined with the tiotropium salt.

Based on the known activities of tiotropium and carmoterol, it was plausible that their combination had some efficacy against the symptoms of respiratory diseases. However, the opposed patent did not provide any experimental data and did not establish proof of any additional technical advantage, such as the "supra-additive" effect alleged by the respondents. On the basis of the information provided in the patent and common general knowledge, it could not be inferred that a therapeutic benefit going beyond a mere additive effect was attained, nor that the efficacy of the claimed combination was different from that of combinations of tiotropium with other LABAs.

The post-published data presented in document D14 could not remedy that lack of evidence for the following reasons:

(i) The improvement purportedly shown in document D14 (i.e. a synergistic or "supra-additive" effect) could not be derived from the patent in suit and the application as filed. As D14 itself was the earliest source of information with regard to the alleged improvement, its data could not be taken into account.

(ii) In any case, the data reported in D14 did not show a synergy of the two drug components tiotropium and carmoterol.

(iii) D14 did not provide a direct comparison with the closest prior art D15, which envisaged combinations of tiotropium with formoterol or salmeterol.

Since it had not been established that the effect of the claimed combination of tiotropium and carmoterol was any different from the effect of combinations of tiotropium with other LABAs such as formoterol or salmeterol, the objective technical problem was the provision of an alternative medicament for the treatment of pulmonary disease.

Document D15 itself suggested combinations of tiotropium with LABAs in general, regarding such combinations as potentially advantageous because of the complementary mechanisms of action of the two classes of drugs. This theoretical rationale was supported by the good practical results which had been obtained with a combination of short-acting agents belonging to the same two classes of actives.

The scope of D15 included novel LABAs with a longer duration of action, comparable to that of tiotropium. Since carmoterol (disclosed in, *inter alia*, documents

D1, D5, D17 and D20) was known as a particularly potent and long-acting novel LABA, it would have been obvious for the person skilled in the art to consider it as a possible combination partner for tiotropium.

Inventive step - auxiliary request

The amendment in claim 1 of the auxiliary request did not change the appellant's position on inventive step since tiotropium bromide, being the commercially available tiotropium salt, was also the salt taught in D15.

XI. The respondents' arguments may be summarised as follows:

Inventive step - main request

The subject-matter of claim 1 differed from the disclosure of document D15 in the specific combination of tiotropium with carmoterol.

The therapeutic activity of each of these compounds was known to the person skilled in the art. As the therapeutic efficacy of the combination was therefore plausible, further evidence of the extent of that efficacy could be taken into account, as provided in post-published document D14.

Document D14 demonstrated a synergistic interaction of tiotropium and carmoterol. Hence, this combination surpassed the state of the art - in particular combinations of tiotropium with formoterol or salmeterol.

Accordingly, the technical problem to be solved was the provision of a combination of tiotropium and a LABA having improved efficacy.

According to D15, combinations of tiotropium with LABA compounds had not been investigated. There was nothing in document D15 to suggest that a combination of tiotropium and carmoterol would be superior in its efficacy to the combinations disclosed in D15, which made specific mention of formoterol and salmeterol only. The secondary prior-art documents disclosing carmoterol cited by the appellant could only have been selected with hindsight of the invention and did not provide any information about the combination of carmoterol with tiotropium.

Inventive step - auxiliary request

The amendment in claim 1 of the auxiliary request was intended to address the appellant's objection concerning added subject-matter and did not change the respondents' arguments on the issue of inventive step.

- XII. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.
- XIII. The respondents (patent proprietors) requested that the appeal be dismissed or, in the alternative, that the patent be maintained in amended form on the basis of the set of claims of the auxiliary request filed with the letter dated 29 July 2014.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is therefore admissible.

2. Inventive step - main request

Patent in suit

2.1 The patent in suit relates to pharmaceutical compositions intended for use in the management of respiratory complaints, particularly chronic obstructive pulmonary disease (COPD) or asthma (see claims 1 and 20 and paragraph [0001] of the patent in suit). In these compositions, carmoterol (the "beta-mimetic of formula 2") is combined with a tiotropium salt, e.g. tiotropium bromide (see claim 4).

2.2 The compounds to be combined according to claim 1 belong to different classes of bronchodilators. Tiotropium is a long-acting muscarinic receptor antagonist (LAMA) anticholinergic, and carmoterol is a long-acting β_2 -adrenoreceptor agonist (LABA). According to the patent in suit, these components may be present in two separate formulations or together in a single formulation. They can be given simultaneously or successively, simultaneous administration being preferred (see claim 2 and paragraphs [0011] to [0013] of the patent).

Starting point in the prior art

2.3 It is common ground that document D15 is a suitable starting point for the assessment of inventive step.

2.4 D15 is a scientific paper which reviews major clinical studies investigating long-acting bronchodilators and discusses the possible benefits of a combination therapy administering tiotropium bromide and LABAs (e.g. salmeterol or formoterol) to patients with COPD. The interest of the authors is explained as follows (see D15: page 270, first paragraph):

"Bronchodilators are the mainstay of therapy for patients with established chronic obstructive pulmonary disease (COPD) but, at present, the majority of patients use short-acting agents. There is increasing evidence that long-acting agents, such as the β_2 -adrenoceptor agonists salmeterol and formoterol, and the new anticholinergic tiotropium bromide provide a better therapeutic option. In the treatment of COPD, long-acting β_2 -adrenoceptor agonists (LABAs) given twice daily cause the same degree of bronchodilation as tiotropium bromide given once daily. Combined use of an inhaled LABA with tiotropium bromide should provide important therapeutic benefits, as these drugs have distinct and complementary pharmacological actions in the airways. Although clinical trials of this combination have not been performed, clinical experience with Combivent, a combination of a short-acting β_2 -adrenoceptor agonist (salbutamol) and a short-acting anticholinergic (ipratropium bromide), in COPD is encouraging because the bronchodilation produced is of a magnitude greater than that of either component alone. However, because LABAs are given twice daily but tiotropium bromide is required only once daily, the challenge is to develop a combined inhaler that can be employed on a daily basis."

2.5 Document D15 does not mention carmoterol.

Objective technical problem and solution

- 2.6 The composition of claim 1 differs from the disclosure of document D15 in that carmoterol is selected as the specific LABA which is to be combined with tiotropium.
- 2.7 The patent in suit does not name a particular advantage of that combination but states that novel compositions for the treatment of inflammatory or obstructive diseases of the respiratory tract, in particular asthma or COPD, are provided. While the patent gives examples of inhalable formulations comprising tiotropium bromide and carmoterol hydrochloride, it does not provide experimental data relating to a technical effect. At the effective date of the patent, it would nevertheless have been expected, based on the known activities of carmoterol and tiotropium, that the claimed combination would be effective against respiratory complaints.
- 2.8 In their submissions in support of an inventive step, the respondents relied on data of an animal study presented in post-published document D14, arguing that the objective technical problem should be formulated as the provision of combinations of tiotropium and LABAs with improved efficacy.
- 2.9 Document D14, which was drafted less than three years after the priority date of the patent in suit, acknowledges the teaching of document D15 (i.e. reference [3] in D14) in favour of combination therapy employing tiotropium and LABAs.

D14 states that carmoterol is a new potent and long-lasting LABA which may be suitable for once-daily treatment and for contemporaneous administration with tiotropium (see D14: page 251, column 1, lines 4 to 26). D14 further reports that evidence was found

of a positive interaction between tiotropium and carmoterol in controlling the bronchoconstriction elicited in guinea-pigs by different challenges (see D14: page 255, column 1, beginning of last paragraph).

D14 explains that the mechanisms by which the bronchodilators achieve smooth muscle relaxation in the airways are different for anticholinergic bronchodilators like tiotropium and β_2 -agonists like carmoterol. Thus, there is potential for the two drugs to have at least an additive effect when used together (see D14: page 254, column 2, "Discussion").

This statement is in agreement with the teaching of document D15 regarding the therapeutic benefit expected from the complementary pharmacological actions of tiotropium and LABAs (see point 2.4 above).

While pointing out that the animal study of D14 was not designed to demonstrate synergism, the finding of a potentiation also when ineffective doses of tiotropium and carmoterol were combined is regarded by the authors of D14 as suggestive of a positive interaction which may be more than additive (see D14: page 255, column 2, lines 6 to 12).

They conclude, however, that this is an aspect yet to be verified as it is not known whether the positive interaction of tiotropium with carmoterol is superior to its interaction with other long-acting LABAs such as formoterol or salmeterol (see D14: page 256, column 1, lines 5 to 13, and the sentence bridging columns 1 and 2):

"Another aspect worthy to be investigated is to verify in the same experimental conditions if the positive interaction is specific for carmoterol and tiotropium combination or is common to other similar combinations, i.e. formoterol or salmeterol and tiotropium,

and carmoterol and another long-acting muscarinic M₃-antagonist. This could be important as the clinical studies with formoterol and salmeterol in combination with tiotropium seem to demonstrate only additive effects."

Thus, D14 arrives at the conclusion that the combination of tiotropium with carmoterol represents another therapeutic option:

"In conclusion, the present results obtained in anaesthetized guinea-pigs strongly suggest that carmoterol and tiotropium combination represents a new therapeutic option for patients affected by increase in airway resistance".

2.10 To summarise, while the experimental results compiled in D14 may suggest that there is a favourable positive interaction between tiotropium and carmoterol, the authors of D14 concede that it had not been verified at the time of writing whether this interaction was specific to the claimed combination and/or achieved a therapeutic benefit largely superior to the effects expected from combinations of tiotropium with formoterol or salmeterol. While mentioning studies with formoterol and salmeterol in combination with tiotropium, document D14 does not actually present data which would allow a direct comparison with combinations of tiotropium and carmoterol. As a consequence, document D14 does not provide conclusive evidence that the combination of tiotropium with carmoterol has superior efficacy.

2.11 It was a subject of dispute between the parties whether document D14 should be taken into account at all in the assessment of the alleged technical effect of the superior efficacy of the claimed combination.

However, this issue can be left undecided as it follows from the above that D14 does not, after all, provide proof of the alleged technical effect but remains on the level of speculation.

2.12 The duration of action of carmoterol did not play a role in the assessment of the technical effects attained by the claimed combination. While the respondents did not contest that carmoterol was known as a LABA with a duration of action not inferior to that of formoterol or salmeterol, they did not rely on a particularly long duration of action in their reasoning in favour of an inventive step, nor is claim 1 restricted to single formulation products suitable for once-daily dosing.

2.13 In the absence of evidence of a specific technical effect of the claimed combination, the objective technical problem to be solved is the provision of an alternative combination of tiotropium with a LABA which may be of use in the management of respiratory complaints.

Obviousness of the solution

2.14 Document D15 teaches that inhaled bronchodilators are the mainstay of therapy for patients with COPD and that short-acting agents (e.g. salbutamol and ipratropium bromide) given four times daily were the most commonly used. The combination product "Combivent[®]", combining the short-acting β_2 -adrenoreceptor agonist salbutamol and the short-acting anticholinergic ipratropium bromide, is mentioned (see D15: page 270, first paragraph, and the paragraph bridging columns 1 and 2).

D15 proposes a combination therapy using longer-acting agents of each type, with the obvious advantage of

better convenience and patient compliance. In particular, tiotropium bromide as a long-acting anticholinergic is to be combined with LABA compounds such as formoterol or salmeterol.

Important therapeutic benefits are expected from the combined use of an inhaled LABA with tiotropium bromide as these drugs have distinct and complementary pharmacological actions in the airways and there is potential for a synergistic effect (see D15: page 270, first paragraph, and page 271, column 1, lines 9 to 14). This rationale is supported by the favourable results obtained by combining short-acting agents of each class in the marketed product "Combivent[®]". Clinical studies with this product showed the superiority of the combined agents over the individual drugs (see D15: page 273, column 1, second paragraph).

It is mentioned that tiotropium bromide is required only once daily. According to D15, conventional available LABAs are usually given twice daily but several novel LABAs with a longer duration of action that would be suitable for inhalation once daily were in development. These would be appropriate for combination with tiotropium bromide in a once-daily inhaler (see D15: page 273, last line of column 1 to column 2, line 5).

- 2.15 Document D15 thus contains a pointer for the person skilled in the art to examine the potential use of further LABA compounds other than formoterol and salmeterol in a combination product with tiotropium bromide.
- 2.16 Although not mentioned specifically in document D15, carmoterol was known to be another LABA compound with potent and particularly long-lasting bronchodilating

activity. Documents D1, D5, D17 and D20 may be cited in this context (see D5: page 1, lines 1 to 8; D1: paragraphs [0035] and [0036]; D17: abstract and page 577, column 1, second paragraph; D20: page 1047, abstract and column 1, first paragraph). Since D15 teaches to consider combinations of tiotropium with further LABAs, it would have been straightforward for the person skilled in the art to follow this advice and consult literature on further LABAs. Hence, the respondents' argument that these documents could only have been consulted in hindsight and with knowledge of the claimed subject-matter must fail.

2.17 The respondents argued that carmoterol was not a "novel" LABA since it had been first developed about two decades before the publication of D15 (see D5). However, it is more plausible that document D15 when referring to "novel LABAs ... in development" meant compounds which had not yet received marketing approval rather than restricting its meaning to include only recently synthesised compounds. Document D1, published less than two years before D15, shows that carmoterol (or TA-2005, see point II above) was at that time being considered as an alternative to formoterol, also in combination with anticholinergics including tiotropium bromide (see D1: paragraphs [0035] and [0036]).

2.18 Thus, the person skilled in the art studying document D15 and seeking to provide alternative combinations would have been directed by D15 to consider other available LABAs for the envisaged combination with tiotropium, would have consulted documents D1, D5, D17 and D20, and thus would have arrived at the subject-matter of claim 1.

- 2.19 For these reasons, the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC.
3. Inventive step - auxiliary request
- 3.1 The tiotropium salt taught in document D15 is tiotropium bromide. Hence, the amendment in claim 1 of the auxiliary request (see point VIII above) does not establish a further technical feature distinguishing the claimed subject-matter from the starting point in the prior art, and the inventive-step assessment set out in section 2 above for claim 1 of the main request remains valid for claim 1 of the auxiliary request.
- 3.2 As a consequence, the subject-matter of claim 1 of the auxiliary request does not involve an inventive step within the meaning of Article 56 EPC.

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