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Datasheet for the decision of 16 November 2021

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Language of the proceedings: EN

Title of invention:
Combination of azelastine and ciclesonide

Patent Proprietor:
Cipla Limited

Opponent:
Sanovel Ilaç San. ve Tic. A.S.

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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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 0132/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 16 November 2021

Appellant: (Opponent)	Sanovel IIaç San. ve Tic. A.S. Balabandere Cad. Ilaç Sanayi Yolu No: 14 Istinye-Sariyer 34460 Istanbul (TR)
Representative:	Wibbelmann, Jobst Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstrasse 2 81541 München (DE)
Respondent: (Patent Proprietor)	Cipla Limited Cipla House Peninsula Business Park Ganpatrao Kadam Marg Lower Parel Mumbai - 400013 (IN)
Representative:	Turner, Craig Robert A.A. Thornton & Co. Octagon Point 5 Cheapside London EC2V 6AA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 November 2017 concerning maintenance of the European Patent No. 2075000 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 2 075 000 (patent in suit) derives from European patent application No. 09 075 100.9 (application as filed), which is a divisional of European patent application No. 03 738 280.1 (parent application, published as international application No. WO 03/105856 A1).

II. The patent in suit was granted with a set of 18 claims. Independent claim 1 reads as follows:

> *"1. A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, and ciclesonide."*

III. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter did not involve an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art and extended beyond the content of both the application and the parent application as filed.

IV. The patent proprietor requested as its main request that the opposition be rejected, and also filed four auxiliary requests. The claims of auxiliary request I were identical to claims 1 to 16 as granted.

V. The documents cited in the course of the opposition proceedings included the following:

D2: Submission dated 20 August 2010, filed by the patent proprietor during the examination proceedings regarding the patent in suit

D6: J Clin Pharmacol 39, 1062-1069 (1999)

D10: EP 0 780 127 A1

D11: Declaration by G. Malhotra including "Exhibit A: Experimental report" (15 December 2016)

VI. The decision under appeal is the opposition division's interlocutory decision, announced on 23 October 2017 and posted on 23 November 2017, finding that the patent as amended in the form of auxiliary request I met the requirements of the EPC.

VII. According to the decision under appeal:

(a) The claims of the patent as granted (main request) did not contain added subject-matter and met the requirements of Articles 76(1) and 123(2) EPC.

(b) They also met the requirement of sufficiency of disclosure (Article 100(b) EPC).

(c) Document D10 represented the closest prior art as it related to nasal sprays containing an antihistamine, which could be azelastine, and a glucocorticosteroid. Starting from the technical teaching of D10, the subject-matter of claims 1 to 16 as granted involved an inventive step, but the subject-matter of claims 17 and 18 as granted did not (Articles 52(1) and 56 EPC).

(d) This objection was overcome by auxiliary request I, in which claims 17 and 18 had been deleted.

Document D10 did not mention ciclesonide but did disclose combining azelastine with budesonide. Taking into account the experimental data provided by the patent proprietor in documents D2 and D11, it was credible that formulations comprising azelastine and ciclesonide (as defined in claim 1) were more stable than corresponding formulations comprising azelastine and budesonide. The objective

technical problem was thus to provide an effective and more stable medicament for the treatment of conditions affecting the eyes and the nose. In view of the structural similarity of ciclesonide and budesonide, the person skilled in the art would not have predicted the improvement in stability. For this reason, the formulations according to claims 1 to 16 of auxiliary request I would not have been an obvious solution.

VIII. The opponent (appellant) appealed against this decision, requesting that the patent be revoked. With the statement setting out the grounds of appeal, the appellant submitted documents D14 to D24. D14 is the opposition appeal decision revoking the patent deriving from the parent application.

D14: T 0609/12

IX. With its reply to the appellant's statement setting out the grounds of appeal, the patent proprietor (respondent) submitted a main request and seven auxiliary requests and filed document D25.

The claims of the **main request** are identical to those of former auxiliary request I held allowable in the decision under appeal (see points II. and IV. above).

Claim 1 of **auxiliary request I** reads as follows:

"1. A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, and ciclesonide, wherein the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request II** reads as follows:

"1. A pharmaceutical formulation which comprises an admixture of azelastine, or a pharmaceutically acceptable salt, ciclesonide and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request III** reads as follows:

"1. A pharmaceutical formulation which is an aqueous suspension or solution comprising azelastine, or a pharmaceutically acceptable salt, and ciclesonide, wherein the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request IV** reads as follows:

"1. A pharmaceutical formulation which comprises an admixture of azelastine, or a pharmaceutically acceptable salt, ciclesonide, and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutically acceptable carrier or excipient comprises microcrystalline cellulose and carboxyl methyl cellulose sodium, and the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request V** reads as follows:

"1. A pharmaceutical formulation which is an aqueous solution or suspension, comprising azelastine, or a pharmaceutically acceptable salt, ciclesonide, microcrystalline cellulose and carboxyl methyl cellulose sodium, and wherein the

pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request VI** reads as follows:

"1. A pharmaceutical formulation which comprises an admixture of azelastine, or a pharmaceutically acceptable salt, ciclesonide and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutically acceptable carrier or excipient comprises microcrystalline cellulose and carboxyl methyl cellulose sodium in an amount of 0.65 to 3.0% by weight of the formulation, and the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

Claim 1 of **auxiliary request VII** reads as follows:

"1. A pharmaceutical formulation which is an aqueous suspension or solution, comprising an admixture of azelastine, or a pharmaceutically acceptable salt, ciclesonide and a pharmaceutically acceptable carrier or excipient, wherein the pharmaceutically acceptable carrier or excipient comprises microcrystalline cellulose and carboxyl methyl cellulose sodium in an amount of 0.65 to 3.0% by weight of the formulation, and the pharmaceutical formulation is in a form suitable for nasal or ocular administration."

X. The appellant's arguments regarding inventive step, as far as relevant to the present decision, may be summarised as follows.

D10 was a suitable starting point for the problem-and-solution approach.

The alleged technical effect of improved stability should be disregarded when defining the technical problem to be solved, for, *inter alia*, the following reasons.

The alleged benefit of better stability could not be conclusively derived from the respondent's post-filed test reports D2 and/or D11 (if these were to be taken into account), nor was it relevant for formulations in which azelastine and the steroid were physically separate.

Moreover, documents D2 and D11 related only to a comparison of the combinations azelastine/ciclesonide and azelastine/budesonide, yet the prior art in example III of D10 also disclosed the preferred combination azelastine/triamcinolone acetonide. No evidence had been provided that this combination was not stable. Even if, as submitted by the respondent, the specific formulation in example III was not showing suitable properties, this drug combination could nevertheless have been tested in a different, more suitable formulation (e.g. such as described in D11).

Accordingly, the objective technical problem had to be formulated as providing an alternative pharmaceutical composition for treating allergic conditions.

Since, at the effective date of the patent in suit, ciclesonide was known (from, *inter alia,* document D6) as a new potent steroid drug in the field of anti-allergy treatments, the person skilled in the art would have contemplated using it as a first and obvious choice.

The appellant did not present any comments concerning the respondent's auxiliary requests.

XI. The respondent's arguments regarding inventive step, as far as relevant to the present decision, may be summarised as follows.

In view of the passage immediately following formulation example III in D10, which included the statement:

> *"Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof."*

any combination of azelastine with triamcinolone, fluticasone, mometasone and budesonide could be considered the closest starting point for the assessment of inventive step. However, because of the structural similarity of budesonide and ciclesonide, the combination of azelastine and budesonide was the most appropriate starting point in document D10.

The stated aim of the invention was to provide a stable and effective combination of azelastine and a steroid (paragraph bridging pages 1 and 2 and paragraph 4 on page 2 of the parent application *[sic]*). Thus, post-filed evidence relating to stability could be taken into account.

As demonstrated by the comparative stability data provided in documents D2 and D11, a pharmaceutical formulation comprising azelastine and ciclesonide was more stable than one comprising azelastine and budesonide derived from the prior art, which showed significant budesonide degradation.

Formulation example III of D10, in which triamcinolone acetonide was combined with azelastine, had been

found by the respondent to be inoperable. In response to the appellant's objection that no evidence had been provided in support of this assertion, reference was made to decision T 0609/12 (D14), the appeal decision issued in respect of the parent application, which included results for example III of D10.

Furthermore, the formulation according to example II of D10 would be expected to be hyperosmotic and unsuitable for nasal or ocular application, due to its excipient composition.

All this suggested that document D10 was unreliable.

Starting from the technical teaching of document D10, the objective technical problem was to provide a more stable and effective pharmaceutical formulation comprising an antihistamine and a glucocorticosteroid.

Document D10 mentioned several choices for the antihistamine, and it did not mention ciclesonide at all as a possible choice for the steroid. Therefore, nothing in D10 would have prompted the person skilled in the art to pick azelastine or its salts as the antihistamine and ciclesonide as the steroid on the expectation of achieving an improvement over the known combinations of antihistamines and corticosteroids.

Document D6 related to ciclesonide monotherapy and did not contain any pointers suggesting combination therapy.

Since budesonide and ciclesonide were structurally similar, the increased stability was an unexpected advantage rendering the claimed formulation inventive. In this context, the patent proprietor did not need to provide any explanation for the observed difference in stability.

Even if the comparative studies D2 and D11 were not to be taken into account, the claimed formulation would still be inventive since the prior art did not teach that the combination of azelastine and ciclesonide was stable and effective, and, in this context, more effective than monotherapy with either drug.

The technical problem should in that case be re-formulated as *"provision of a combination of an antihistamine and a glucocorticosteroid having a rapid onset of action and quick relief"*.

XII. The board issued a summons inviting the parties to attend oral proceedings.

In a communication under Article 15(1) RPBA the board advised the parties of its preliminary opinion, *inter alia* setting out some of the inventive-step issues which might require consideration at the oral proceedings. These included the appellant's argument that a comparison with the combination of azelastine and triamcinolone acetonide should have been made (see point 3.4.2 of the communication).

The communication also pointed out that none of auxiliary requests I to VIII had been presented during the proceedings before the opposition division, and that the respondent had not explained the purpose of these new requests, i.e. how they might address any argument raised by the appellant (see point 4.1 of the communication).

XIII. By letter dated 26 March 2021, the appellant's representative withdrew the appellant's request for oral proceedings and stated that it would not be attending the oral proceedings scheduled for 10 June 2021.

XIV. By letter dated 1 June 2021, the respondent indicated it would not be attending the oral proceedings.

XV. Neither party replied in substance to the board's preliminary opinion.

XVI. The board cancelled the oral proceedings and advised the parties that the appeal proceedings would be continued in writing.

XVII. This decision is based on the following requests by the parties:

(a) The appellant (opponent) requested that the decision under appeal be set aside and the patent in suit be revoked.

Within the purview of these requests, the appellant also requested that documents D15 to D24 be admitted into the proceedings.

(b) The respondent (patent proprietor) requested that the appeal be dismissed and that the patent be maintained in the amended form upheld by the opposition division (main request);

or, in the alternative, that the patent be maintained according to one of auxiliary requests I to VII, all filed with the reply to the statement setting out the grounds of appeal.

Within the purview of these requests, the respondent also requested that documents D15 to D24 not be admitted, but that document D25 be admitted into the proceedings.

Reasons for the Decision

1. Admissibility of the appeal

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

2. Main request - inventive step (Articles 100(a), 52(1) and 56 EPC)

Patent in suit

2.1 The patent in suit seeks to provide formulations combining the effects of antihistamine treatments and corticosteroid treatments, preferably for nasal or ocular administration (see paragraphs [0001] and [0005] of the patent). Azelastine is to be used as the antihistamine (see claim 1).

2.2 The patent in suit also contains the following statement (see paragraph [0006]):

> *"We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexa-hydro-1-methyl-1H-azepin-4-yl)-1(2H)pthalazinone), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably in salt form and even more preferably in the form of the hydrochloride salt, can advantageously be combined with a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, to provide a stable, very effective combination product or formulation preferably for nasal or ocular treatment. The combination can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and*

the anti-inflammatory (and/or other) properties of the steroid, without any significant interference between the two, or adverse reaction in situ."

Combinations of azelastine with various steroids are mentioned in the description (see paragraphs [0008], [0094], examples 2-14).

2.3 Claim 1 of the main request defines a pharmaceutical formulation comprising azelastine or a pharmaceutically acceptable salt (presumably of azelastine) as the antihistamine, and ciclesonide as the steroid.

Starting point in the prior art

2.4 It is common ground that document D10, which is concerned with treating allergic disorders, in particular allergic rhinoconjunctivitis, is a suitable starting point for the assessment of inventive step.

2.5 D10 relates to nasal spray compositions containing a glucocorticoid (corticosteroid) and a leukotriene-inhibiting antihistamine selected from cetirizine, loratadine, azelastine, pharmaceutically acceptable salts or racemates thereof or mixtures thereof. The steroid may be beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide or pharmaceutically acceptable salts thereof or mixtures thereof (see D10: claim 1 and page 2, lines 5 to 6 and 25 to 27). Ciclesonide is not mentioned.

2.6 Example III of D10 discloses a specific formulation comprising azelastine hydrochloride and triamcinolone acetonide, various excipients and water, to be used for topical nasal application to provide relief from allergy or allergy-like symptoms. Immediately following

this disclosure it is also mentioned that (D10: page 6, lines 26 to 46):

> *"Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof."*

2.7 Hence, combinations of azelastine with triamcinolone acetonide, fluticasone, mometasone or budesonide are disclosed in D10 at the same level of preference.

Objective technical problem and solution

2.8 The formulation according to claim 1 of the main request differs from these prior-art formulations in that it uses ciclesonide as the steroid combination partner of azelastine.

2.9 According to the respondent, this has the advantage that the claimed combination of azelastine and ciclesonide is more stable than the combination of azelastine and budesonide, as supported by the comparative studies reported in D2 and D11.

2.10 While the application as filed states that combining azelastine with steroids will provide stable and effective formulations, it neither suggests that the combination of azelastine with ciclesonide is more stable than other combinations nor contains any experimental data on stability. The appellant therefore questioned whether it was appropriate to take post-filed data into account.

2.11 Irrespective of this issue, however, and as also pointed out by the appellant, the combination of azelastine with budesonide is not the only comparative

combination to be considered. The combination of azelastine with triamcinolone acetonide is an equally legitimate starting point in the prior art (see point 2.7 above).

2.12 A perceived closer structural similarity of budesonide with ciclesonide is not a convincing reason for ruling out the combination of azelastine with triamcinolone acetonide (or, indeed, with fluticasone or mometasone) as another feasible starting point, nor does it remove the requirement to demonstrate the alleged technical effect in relation to that alternative starting point. If it were shown (as argued by the respondent) that the combination of azelastine with budesonide is less stable than the combination of azelastine with ciclesonide, it would not necessarily follow that the combination of azelastine with other steroids such as triamcinolone acetonide has the same disadvantage.

2.13 The respondent's verbal statement that example III of D10 was found to be *"an unworkable and inoperable pharmaceutical formulation"* (see the reply to the appellant's statement of grounds, page 31, fifth paragraph) is not sufficient on its own to demonstrate that the combination of azelastine with triamcinolone is inferior to its combination with ciclesonide, for want of any disclosure of the actual experiment that was carried out and the results that led to the respondent's conclusion. Without this information it cannot be verified whether there is a particular problem with the formulation of example III which can be attributed specifically to triamcinolone acetonide (and/or its combination with azelastine) rather than other formulation components.

2.14 In this context, the respondent also made the following statement (see the reply to the appellant's statement of grounds, page 31, last paragraph):

> *"The Opponent has indicated that we did not provide any evidence in support of the fact the example III of D10 was found inoperable. However, the Opponent has now referred to D14 the decision issued in respect of the parent application, which includes results of the example III of D10."*

2.15 While it is questionable in any case whether a sweeping reference to the decision in another appeal case can be deemed acceptable substantiation when dealing with this kind of concern, it is also apparent from perusing the decision in question that it does not provide the information needed.

2.16 The respondent's argument that the formulation of example II of D10 (which does not contain azelastine) would be expected to have unsuitable osmolality due to its excipient composition is not relevant to the issue of comparing the properties of formulations combining azelastine with varying steroids.

2.17 Since there are no conclusive comparative data on file with regard to the combination of azelastine with triamcinolone acetonide, the alleged technical effect of better stability has not been demonstrated in relation to this alternative starting point.

2.18 Starting from the formulation containing azelastine hydrochloride and triamcinolone acetonide in example III of document D10, the objective technical problem therefore has to be formulated as providing an alternative pharmaceutical formulation comprising a combination of azelastine and a corticosteroid.

2.19 It was not in dispute that the claimed formulation solves this technical problem.

Obviousness of the solution

2.20 In order to solve the objective technical problem, the person skilled in the art would have consulted literature about steroids effective in treating allergic disorders affecting the nose and eyes, such as document D6. It would not have been essential for this purpose that the documents consulted for information about steroids also refer to combination therapies.

2.21 Ciclesonide was known at the relevant date as a recently developed topical corticosteroid effective in treating allergic rhinitis (see D6: abstract; page 1063, left-hand column; page 1069, last paragraph).

2.22 On this basis, the person skilled in the art would have regarded ciclesonide as a promising and obvious further option for the choice of steroid.

2.23 The respondent's argument that nothing in D10 would have prompted the person skilled in the art to pick azelastine or its salts as the antihistamine to provide a more stable formulation is not consistent with the objective technical problem (see point 2.18 above) or with the respondent's own suggestion regarding the starting point in D10 (namely a formulation that already includes azelastine; see point XI. above). It is not convincing either. Article 56 EPC requires an invention to be be non-obvious with regard to the prior art, i.e. every piece of prior art. It is therefore appropriate to select a specific embodiment in a document as the most promising starting point in the context of the problem-and-solution approach (in this

case: formulations containing azelastine or its salts; see points 2.6 and 2.7 above).

2.24 The respondent further contended that even if better stability were not recognised as a technical effect of the claimed formulations, it would nevertheless have been considered a surprising benefit that the combination of azelastine and ciclesonide, which was not disclosed as such in the prior art, turned out to be stable and effective.

2.25 This argument cannot succeed, for the following reasons.

2.25.1 While this particular drug combination is not suggested in D10, it would nevertheless have been expected to show efficacy in the intended treatment since the therapeutic utility of both azelastine and ciclesonide on their own for treating conditions of the eyes and nose, such as rhinitis and conjunctivitis, was known (as acknowledged by the respondent in the reply to the statement setting out the grounds of appeal, page 17, fifth paragraph).

2.25.2 The respondent's further assertion that the combination of azelastine and ciclesonide was found to have better efficacy (in terms of rapid onset of action and quick relief from symptoms) than monotherapy with either drug is not relevant in this context, since it does not relate to a comparison with the starting point in the prior art (see points 2.7 and 2.8 above) and thus it does not follow the problem-and-solution approach. Hence, it is not permissible, either, to re-formulate the technical problem as *"provision of a combination of an antihistamine and a glucocorticosteroid having a rapid onset of action and quick relief"*, as suggested by the respondent.

2.25.3 Furthermore, it has not been shown that the person skilled in the art would have had any specific reason to fear a lack of stability or compatibility with regard to the combination of azelastine and ciclesonide. This was also the respondent's own argument when discussing the issue of post-filed evidence (reply to the statement setting out the grounds of appeal, page 18, first sentence).

2.26 For these reasons, the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

3. Auxiliary requests I to VII

3.1 Auxiliary requests I to VII were filed for the first time with the respondent's reply to the statement setting out the grounds of appeal (see points IX. and XII. above).

3.2 The respondent did not explain the purpose of these requests, merely remarking in a general way that each of the auxiliary requests had been filed in response to the appellant's newly filed documents and to the appellant's argument that the alleged technical effect did not provide improvement across the entire scope claimed. No specific explanation was given as to how each request might address any particular inventive-step argument raised by the appellant. The respondent furthermore stated that its comments made in relation to the main request were equally applicable in relation to the auxiliary requests.

3.3 It is not apparent how the various technical features added to claim 1 of each auxiliary request might provide a contribution to inventive step, not did the respondent provide any substantiation in this regard. Therefore, the reasoning on the inventive step of

claim 1 of the main request set out in section 2 above equally applies to claim 1 of each of auxiliary requests I to VII.

3.4 In conclusion, the subject-matter of claim 1 of each of auxiliary requests I to VII does not involve an inventive step within the meaning of Article 56 EPC.

4. Admittance of evidence

4.1 The board's reasoning set out above does not rely on any of documents D15 to D24 filed by the appellant (see point VIII. above).

4.2 Hence, a decision regarding the admittance of documents D15 to D24 under Article 12(4) RPBA-2007 is not required as they are irrelevant to the outcome of the appeal case in the appellant's favour.

4.3 Document D25 filed by the respondent relates to certain excipents used according to D11 and could have no relevance to the board's line of reasoning pursued in points 2.17 ff above.

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