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**Datasheet for the decision
of 11 December 2015**

Case Number: T 1677/12 - 3.3.07

Application Number: 05824835.2

Publication Number: 1827499

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Language of the proceedings: EN

Title of invention:

COMPOSITIONS COMPRISING AZELASTINE AND METHODS OF USE THEREOF

Applicant:

Meda Pharmaceuticals Inc.

Relevant legal provisions:

RPBA Art. 13(1)

EPC Art. 56

Keyword:

Admission of new request

Inventive step - (no)



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Case Number: T 1677/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 December 2015

Appellant: Meda Pharmaceuticals Inc.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted on 23 February
2012 refusing European patent application No.
05824835.2 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman A. Uselli
Members: R. Hauss
P. Schmitz

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division, pronounced on 9 February 2012 and posted on 23 February 2012, refusing European patent application No. 05 824 835.2.
- II. The documents cited in the course of the examination and appeal proceedings include the following:
- D1: US 2002/0037297 A1
 - D8: US 2004/0115133 A1
 - D9: US 5164194 A
 - D10: US 2002/0120014 A1
 - D11: US 2002/0197327 A1
 - D14: Declaration of Harry J. Sacks, M.D. under 37 C.F.R. §1.132 (11 November 2009)
 - D15: Second declaration of Harry Sacks, M.D. (25 October 2010)
 - D16: Declaration of Alexander D. D'Addio, Ph.D. under 37 C.F.R. §1.132 (29 April 2011)
 - D17: Second declaration of Alexander D. D'Addio, Ph.D. (9/6/11)
 - D18: Declaration of Warner Carr, MD under 37 C.F.R. §1.132 (10-12-10)
 - D19: Declaration of James A. Hadley, MD, FACS under 37 C.F.R. §1.132 (11 October 2010)
 - D20: Declaration of Phil Lieberman, M.D. under 37 C.F.R. §1.132 (11 October 2010)
- Documents D10 to D20 were annexed to the appellant's letter dated 13 November 2015.
- III. The decision under appeal was based on a main request and two auxiliary requests.

The examining division found that the claims of the main request and first auxiliary request defined subject-matter extending beyond the content of the application as filed (Article 123(2) EPC).

Claim 1 of the second auxiliary request was based on example 1 of the application and related to a specific pharmaceutical composition for intranasal administration comprising azelastine hydrochloride, sucralose, sorbitol and further specified components. Starting from example composition 1 of prior-art document D1 (a nasal spray containing azelastine hydrochloride and sorbitol), the technical problem was defined as providing an alternative composition comprising azelastine hydrochloride. The use of 0.1 to 5% sweeteners such as sucralose and/or sorbitol for masking the bitter taste of nasal drops was known from document D8. The skilled person aiming to solve the technical problem would routinely have adjusted the concentrations and would have added sucralose in an amount as disclosed in D8, thereby arriving at the subject-matter of claim 1, which therefore did not involve an inventive step (Article 56 EPC).

- IV. The applicant (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal, the appellant also submitted an amended main request and a first auxiliary request. In both requests, claim 1 was based on example 1 of the application.

- V. In a communication issued in preparation for oral proceedings and advising the appellant of the board's preliminary opinion, the board observed that, due to objections under Articles 123(2) and 84 EPC, neither of the then pending requests appeared to be allowable.

The board furthermore considered that document D9, cited in the application, which disclosed a nasal formulation of azelastine hydrochloride comprising sorbitol, was suitable as a starting point for the assessment of inventive step. The technical problem might be defined as the provision of an alternative nasal formulation of azelastine hydrochloride, or possibly as the provision of such a formulation having a more pleasant taste. Either problem was solved by the addition of sucralose to the formulation and an increase in the concentration of sorbitol, accompanied by other minor variations in the composition. In the light of prior-art document D8 which disclosed sorbitol and sucralose as suitable excipients for taste-masking and sweetening in intranasal dosage forms, that solution did not appear to involve an inventive step.

VI. With letter dated 13 November 2015, the appellant submitted a second auxiliary request, further arguments and a number of documents including D10 to D20.

Claim 1 of the second auxiliary request reads as follows:

"1. A pharmaceutical composition in the form of a nasal solution consisting of:

0.15% (w/v) azelastine hydrochloride;
0.1% (w/v) hypromellose 2900 USP 4000;
0.05% (w/v) disodium edetate;
0.025% (w/v) benzalkonium chloride 50%;
0.15% (w/v) sucralose;
6.4% (w/v) sorbitol 70%;
0.068% (w/v) sodium citrate dihydrate;
and QS water."

VII. In oral proceedings held on 11 December 2015, the appellant withdrew the former main request and first

auxiliary request and maintained the former second auxiliary request as its sole claim request.

VIII. The appellant's arguments with regard to inventive step can be summarised as follows:

Document D9, which was the closest prior art, taught that nasal administration of azelastine solved the problem of bitter taste. Based on that teaching, the person skilled in the art would therefore have had no motivation to add taste-masking agents or sweeteners to the compositions of D9.

The technical problem to be solved related to the provision of a nasal formulation of azelastine to address issues of bitterness which previously had not been appreciated, whilst maintaining efficacy and avoiding insolubility and other formulation issues.

The formulation according to claim 1, which combined azelastine hydrochloride with sorbitol and sucralose in a nasal solution, addressed the problem of bitterness which was well known to patients and healthcare providers, thus fulfilling a long-felt need.

Moreover, as evidenced by declarations D14 to D17, the claimed formulation surprisingly showed better than expected therapeutic efficacy. Even though the technical effect of increased efficacy was not mentioned in the application as filed, the technical problem could be reformulated on the basis of new experimental data.

The combination of azelastine hydrochloride with sucralose and sorbitol, as defined in claim 1, could not be derived from the teaching of document D8, which related to a different class of active agents and mentioned numerous sweeteners, flavouring agents or taste-masking agents. Moreover, it was known from

prior-art documents D10 (paragraph [0058]) and D11 (paragraph [0006]) that artificial sweeteners like sucralose had a bitter taste and were ineffective at masking strongly bitter drugs. Since numerous different possibilities of addressing a bitterness problem could be envisaged, solving that problem was not straightforward and involved extensive non-routine experimental work, especially as the effect of flavour additives was not predictable and could only be evaluated by tasting the formulations.

- IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the request previously submitted as the second auxiliary request with letter of 13 November 2015, and now its sole request, or alternatively that the case be remitted to the examining division for further consideration of any remaining formal issues.

Reasons for the Decision

1. Admission of a new request (Rule 13(1) RPBA)
 - 1.1 The request filed with the appellant's letter of 13 November 2015 as the second auxiliary request was submitted in reply to the board's communication (see point V above), to overcome objections under Articles 123(2) and 84 EPC. It does not change the factual basis of the discussion on inventive step.
 - 1.2 Hence the board considers it appropriate to admit the new request into the proceedings. Since the former main request and first auxiliary request were withdrawn, the former second auxiliary request is now the sole claim

request to be examined (see point VI above for the wording of claim 1).

2. Inventive step (Articles 52(1) and 56 EPC)

Application

2.1 The present application seeks to provide a therapeutically effective dosage form of azelastine hydrochloride, i.a. for nasal delivery, with a better taste and/or less tendency to drip down into the pharynx after administration (see paragraph [0006]). These desired properties are provided by the addition of sweeteners/taste-masking agents and by the addition of thickeners to the formulations (see paragraphs [0008] and [0009] of the application).

Starting point in the prior art

2.2 Azelastine and its salts, their pharmacological effects and the concept of intranasal application of those actives were previously known. In that context (see paragraphs [0002] to [0005]), the present application refers to document D9.

2.3 The appellant agreed that D9 was the closest prior art among the references cited (see its letter of 13 November 2015, page 3).

2.4 Document D9 proposes the intranasal or intraocular application of azelastine or its salts (D9: column 1, lines 34 to 38).

In example 1, D9 discloses a formulation suitable as nasal spray, nasal drops or eye drops, consisting of 0.1% (w/v) azelastine hydrochloride, 0.1% hydroxypropyl methylcellulose (hypromellose), 0.05% disodium edetate dihydrate, 0.0125% benzalkonium chloride, 0.0438% citric

acid, 0.68% sodium chloride and 0.648% sodium monohydrogen phosphate dodecahydrate in water. In that formulation, the sodium chloride, which is used as an isotonicity agent, may be replaced by 3.84% sorbitol (D9: column 4, lines 30 to 49). That constitutes a direct disclosure of an alternative embodiment of the formulation according to example 1, which contains 3.84% sorbitol instead of 0.68% sodium chloride. Due to its similarity in terms of technical features with the claimed composition, this embodiment of D9 is regarded as the most suitable starting point for the assessment of inventive step.

It may be added in this context that sorbitol disclosed in example 1 of D9 is not an untypical ingredient, as it was known in the art as an isotonicity agent (see D9: column 4, lines 30 to 50, D1: example 1 and paragraph [0020], present application: paragraph [0078]).

According to D9 (column 4, lines 50 to 67), thickening agents such as hypromellose are used to render the composition more viscous to prevent it from flowing out of the nose too quickly after application.

Document D9 also mentions that the exceptionally penetrating bitter taste of azelastine, unfavourable to oral application, is no longer in evidence when the azelastine formulations of D9 are sprayed into the nose. D9 adds that "moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx" (D9: column 1, line 56 to column 2, line 2). Thus the reader of D9 would have been aware that a bitter taste is, to some extent, still perceptible with intranasal application.

Technical effects, technical problem and solution

- 2.5 The composition defined in present claim 1 differs from the composition of example 1 according to D9 (with 3.84% sorbitol as defined in column 4, line 48 of D9) in the presence of sucralose, the absence of sodium monohydrogen phosphate and some differences in the concentrations of the other components, sorbitol being present at 4.48%.
- 2.6 According to the appellant, the claimed composition, due to combining azelastine hydrochloride with sucralose and sorbitol, provides two technical effects on which inventive step is based, one being taste improvement and the other an increase in therapeutical efficacy.
- 2.7 Taste improvement
- 2.7.1 It is mentioned in the present application (see page 3, lines 3 to 7) that the bitter taste of azelastine hydrochloride may still be an undesired element, as a portion of the medicament usually drips down into the pharynx after intranasal administration, leading to an unpleasant taste experience by the patient.
- 2.7.2 The alleged technical effect of the use of taste-masking agents (i.a., sucralose and sorbitol are mentioned), used alone or in combinations of two or more such agents, consists in masking the bitter taste associated with azelastine, thus enhancing the organoleptic acceptance of the composition when applied to the nasal mucosa (see page 4: paragraph [0008]; pages 18 to 19: paragraph [0069] to [0070]) of the application). It is mentioned that in preferred embodiments the taste-masking agent is sucralose. In a different passage of the application, sorbitol is also mentioned as an isotonicity agent (paragraph [0078]; see also D16: point 13).

2.7.3 While the appellant has not provided experimental data comparing the claimed composition with the closest composition of document D9 (viz. the composition of example 1 containing sorbitol), the board accepts in the appellant's favour that an improvement in taste may be achieved with the claimed formulation, whether in comparison with a corresponding formulation not containing sucralose or in comparison with such a formulation containing neither sucralose nor sorbitol. Since both sucralose and sorbitol are generally known as sweeteners, it is credible that the bitter taste of azelastine hydrochloride may be reduced or masked in the formulation of claim 1 containing both compounds, and that this may be the case even at a higher concentration of active agent (in the present case, 0.15% vs. 0.1%).

2.8 Increase in therapeutical efficacy

2.8.1 The appellant furthermore argued, with reference to a clinical study on efficacy which is discussed in declarations D14 to D17 (see D14: points 19, 27, 28; D15: points 7 to 13, D16: points 15 and 16; D17), that the combination of azelastine hydrochloride with sucralose and sorbitol showed increased efficacy relative to a composition comprising azelastine hydrochloride without these two sweeteners.

2.8.2 That study does not, however, provide an adequate comparison with a formulation reflecting the closest prior art, i.e. containing azelastine hydrochloride in the presence of sorbitol (representative of example 1 of D9 with column 4, line 48). Moreover, since the complete qualitative and quantitative composition of the formulations employed in the comparative study has not been detailed, it cannot be verified if further differences between the tested compositions existed.

- 2.8.3 As the observed increase in efficacy has therefore not been shown to have its origin in a distinguishing feature of the claimed subject-matter compared with the closest prior art, it cannot be taken into account in the definition of the technical problem.
- 2.9 No particular technical effect has been associated with the choice of any excipient other than sucralose and sorbitol or with the variations in the concentrations of the excipients (see point 2.5 above), and the appellant has not based any argument in support of inventive step on such features.
- 2.10 Starting from the teaching of document D9, in particular from example 1 of D9, and taking into account the considerations set out in section 2.7 above, the technical problem is thus defined as the provision of a nasal formulation of azelastine hydrochloride having a more pleasant taste.
- 2.11 The solution to that problem consists in the composition as defined in present claim 1.

Obviousness of the solution

- 2.12 Document D8 addresses the problem of sweetening and taste masking in intranasal dosage forms to improve patient compliance, and discloses that sorbitol and sucralose are suitable excipients for that purpose (D8: paragraphs [0012], [0035] to [0037]). The sweetener or flavouring agent is supposed to mask any bitter or unpleasant taste that may occur if the pharmaceutical composition drips back into the mouth after intranasal administration (see D8: paragraph [0035]).
- 2.13 The appellant argued that, according to the teaching of document D9 (column 1, lines 63 ff), the problem of

bitterness in formulations containing azelastine was solved by nasal administration, so that in view of this teaching the person skilled in the art would have had no reason to try to improve the taste of the formulations and would not have consulted document D8. The step of identifying that there still existed a problem of residual bitterness was part of the appellant's invention.

2.14 The board does not reach that conclusion, for the following reasons:

- Document D9 itself acknowledges that a bitter taste may still be perceptible when the sprayed azelastine solution or suspension runs down into the pharynx (D9: column 1, line 56 to column 2, line 2). The appellant's argument that the words "barely perceptible" used in D9 mean "to such a minimal extent as to be insignificant", and that the reader of D9 would have considered that the bitterness of azelastine was no longer a problem when it was administered nasally, is not convincing. While document D9 basically reports an improvement in taste which was found with nasal administration in comparison with oral administration, it does not mention the number of trial subjects and does not examine whether the "barely perceptible" residual taste is insignificant to most subjects.

- Furthermore, it is evident from the various statements by medical practitioners which were submitted by the appellant that azelastine in liquid nasal formulations had long been known to be bitter (see D18: points 8, 9; D19: points 8 to 10; D20: points 8, 10, 11, 15). For instance, in the case of the appellant's commercial product "Astelin", a nasal solution containing azelastine hydrochloride, it was well known before the priority date of the application that about 20% of

patients complained about bitterness. This was also mentioned in package inserts and medical literature. During the oral proceedings before the board, the appellant conceded that the bitterness problem was known.

Hence, the board finds that the above-mentioned technical problem of providing a nasal formulation of azelastine hydrochloride having a more pleasant taste derives from D9 alone or together with the skilled person's general knowledge at the priority date of the application. The invention is therefore not based on the discovery of an unrecognised problem, as initially argued by the appellant. In order to solve the technical problem, the person skilled in the art would certainly have had reason to consult documents dealing with the problem of masking a bitter taste in nasal formulations, such as D8.

2.15 The appellant also contended that the person skilled in the art would not have assumed that the addition of sucralose and sorbitol suggested in document D8 would successfully improve the taste of formulations containing azelastine hydrochloride, since D8 related to a different class of active agents (viz. opioids) and mentioned many possible choices of sweeteners, and since it was known from prior-art documents D10 (paragraph [0058]) and D11 (paragraph [0006]) that artificial sweeteners like sucralose had a bitter taste and were ineffective at masking strongly bitter drugs.

2.16 The board is not convinced by these arguments, for the following reasons:

- Although document D8 focuses on formulations containing opioids, it does not suggest at any point that the sweeteners or taste-masking agents mentioned

would specifically interact with opioids, or that they would not be effective when combined with different active agents (see D8: paragraphs [0035] to [0037]).

- While D8 mentions lists of sweeteners, flavouring agents or masking agents, all of those components are presented as possible choices for improving a bitter taste. A merely arbitrary choice from a number of possible solutions requires no inventive skill.

- Contrary to the appellant's view, the cited passages of D10 and D11 do not prove a technical prejudice against using sucralose or sorbitol, both well-known sweeteners, as taste-improving agents:

- a) The first passage (D10: paragraph [0058]) mentions that the use of certain substances in oral care products may lead to unpleasant, especially bitter, taste impressions. Sweeteners are, *inter alia*, mentioned as possible examples of such substances, with sorbitol and sucralose mentioned, among other compounds, in a list of examples of sweeteners. This statement does not necessarily imply that sorbitol and sucralose produce a bitter taste, since it is not indicated whether all the compounds listed in D10 as examples of sweeteners have an undesirable taste. Still less can it be inferred that sorbitol or sucralose inevitably have a bitter or otherwise intolerably unpleasant taste. Moreover, an unpleasant taste in an oral product might also be "too sweet". Thus, the cited passage remains inconclusive.
- b) The second passage (D11: paragraph [0006]) merely states in a general way that sweeteners may not always be sufficient to mask a bitter taste:
"...where the active agent possesses a particularly

strong or bitter taste, such as is the case with many antibiotics, the mere addition of such flavoring agents and sweeteners is insufficient to improve taste and palatability." The board fails to see the relevance of this statement to the present case, since it does not permit any conclusion to be drawn as to whether sucralose and sorbitol would be sufficient to mask the bitter taste of azelastine hydrochloride.

- 2.17 The appellant also held that non-routine extensive experimental work had been necessary to develop the formulation according to claim 1, *inter alia* with regard to selecting the appropriate bitterness-reducing measures from many possibilities, and to maintaining product properties like solubility and efficacy.
- 2.18 However, the fact that different solutions to the problem of bitterness could have been imagined and were indeed tested during a long development phase (such as trying different salts or encapsulated forms of the active agent) does not render the proposed solution, which represents one of several available choices, inventive. The decisive point is that it was known from the teaching of document D8 that sucralose and sorbitol are taste-improving excipients suitable for use in intranasal formulations. Starting from the teaching of D9, and in order to achieve a more pleasant taste, the skilled person would accordingly add sweeteners and taste-masking agents known as suitable for intranasal application and/or increase their concentrations. It has not been credibly shown that a technical prejudice existed against choosing sucralose or sorbitol for that purpose. Thus the person skilled in the art, by combining the teaching of document D9 with that of D8 in order to solve the technical problem, would arrive at

the subject-matter defined in claim 1 without the exercise of inventive skill.

Optimising the formulation to maintain properties like solubility, tonicity or efficacy, although potentially involving extensive experimental work, would be routine for the skilled formulator.

- 2.19 Since no particular technical effect has been associated with the choice of any excipient other than sucralose and sorbitol or with the variations in the concentrations of the excipients (see point 2.9 above), those features are regarded as routine adaptations of the formulation (e.g. with a view to pH and tonicity) or arbitrary modifications not relevant to inventive step.
- 2.20 As a consequence, the subject-matter defined in claim 1 does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



G. Rauh

A. Usuelli

Decision electronically authenticated