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Datasheet for the decision of 21 November 2017

Case Number: T 0326/15 - 3.3.07

Application Number: 03766387.9

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Title of invention:
ORAL ADMINISTRATION OF CALCITONIN

Applicant:
Novartis AG

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 0326/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 November 2017

Appellant: (Applicant)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Fabry, Bernd IP2 Patentanwalts GmbH Schlossstrasse 523 41238 Mönchengladbach (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 9 October 2014 refusing European patent application No. 03766387.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	R. Hauss
	I. Beckedorf

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division, announced on 2 October 2014 and posted on 9 October 2014, refusing European patent application No. 03766387.9. The decision under appeal was based on a main request and an auxiliary request.

Claim 1 of the main request reads as follows:

"1. A pharmaceutical composition comprising

(a) calcitonin in combination with

(b) one or more oral delivery agents selected from N-(5-chlorosalicyloyl)-8-amino caprylic acid, N-(10-[2-hydroxybenzoyl]aminodecanoic acid or N-(8-[2-hydroxybenzoyl]amino)caprylic acid, or a disodium salt, hydrate or solvate thereof,

for use in the treatment of a disorder responsive to the action of calcitonin, wherein said composition is administered orally to a human host from 15 minutes to 30 minutes prior to a meal."

The wording of **claim 1 of the auxiliary request** is identical to that of claim 1 of the main request, except that the definition of component (b) reads as follows:

"(b) N-(5-chlorosalicyloyl)-8-amino caprylic acid disodium salt as an oral delivery agent,"

II. The documents cited in the course of the examination proceedings included the following:

D1: WO 00/59480 A1
D2: WO 02/45754 A2

III. In the decision under appeal, the examining division found that the subject-matter of claim 1 of the main request did not involve an inventive step within the meaning of Article 56 EPC.

Either one of documents D1 and D2, which disclosed oral compositions containing calcitonin and (di)sodium salt of N-(5-chlorosalicyloyl)-8-amino caprylic acid, could be considered as the closest prior art.

The subject-matter of claim 1 differed from the disclosure of document D1 in that the composition was to be administered to a human subject 30 to 15 minutes prior to a meal. As could be inferred from the test data presented in example 7 of the application, pre-meal administration gave rise to higher bioavailability of calcitonin than administration with a meal.
The technical problem to be solved was optimising the bioavailability of oral compositions comprising calcitonin. Since it was well known that food intake could affect bioavailability, the person skilled in the art would have studied this food effect, as for any new drug formulation, and would thus have identified the advantage of pre-meal administration. On that basis, the selection of the claimed dosage regime did not require inventive skill.

The same reasoning applied to claim 1 of the auxiliary request. The selection of a specific compound as the delivery agent, which was also a preferred delivery agent in the prior art, did not contribute anything to inventive step, the applicant having stated previously that the nature of the delivery agent was not critical for the invention.

IV. The applicant (appellant) lodged an appeal against that decision.

V. With the statement setting out the grounds of appeal filed with letter dated 4 February 2015, the appellant submitted two sets of claims as main request and auxiliary request. The main request is identical to the main request considered in the decision under appeal. Claim 1 of the auxiliary request is identical to claim 1 of the auxiliary request considered in the decision under appeal.

VI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or first auxiliary request, both filed with letter of 4 February 2015.

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

Starting from the technical teaching of documents D1 or D2, the technical problem to be solved was to identify conditions under which the bioavailability of calcitonin, when administered orally together with a suitable delivery agent, reached an optimal value.

The dosage regime according to claim 1 of the main request, requiring that the pharmaceutical composition be administered within an interval of exactly 30 to 15 minutes prior to a meal, was inventive, since the prior art did not even teach whether oral calcitonin should be administered before, during or after a meal to optimise bioavailability.

Prior to the invention, no orally bioavailable peptides had been approved by the US Food and Drug Administration or the European Medicines Agency, nor had the effect of food intake on the bioavailability and efficacy of oral peptide formulations been systematically investigated at all, as corroborated by document D4 (Br J Clin Pharmacol 87(4), 413 ff (2009)).

Furthermore, the dosage regime according to claim 1 would have been regarded as counter-intuitive by the person skilled in the art, who would have been aware that calcitonin had an anti-resorptive effect but a short half-life in serum, and that bone resorption had a strong circadian variation with peak levels occurring during the night. Prior to the invention, the administration of calcitonin in the evening (thus, with or after an evening meal rather than prior to a meal) would therefore have been regarded as a possible way of ensuring maximum clinical benefit.

VIII. In a communication issued in preparation for oral proceedings, the board gave a negative preliminary opinion on inventive step.

IX. With letter of 24 October 2017, the appellant informed the board that it would not be attending the oral proceedings scheduled for 21 November 2017 and requested a decision according to the state of the file. It did not provide any further arguments in reply to the board's communication.

X. Oral proceedings were held on 21 November 2017 in the absence of the appellant, in accordance with Article 15(3) RPBA and Rule 115(2) EPC.

Reasons for the Decision

1. Inventive step - main request

Present application

1.1 The present application seeks to provide a medicament for the treatment of disorders responsive to the action of calcitonin with an oral dosage regime achieving good

bioavailability (see page 1, paragraph 1; page 4, paragraph 1 of the description).

1.2 The solution defined in claim 1 of the main request for achieving that aim involves the selection of a dosage regime wherein a pharmaceutical composition comprising calcitonin (component (a)) and one or more agents known to facilitate calcitonin absorption (delivery agents according to component (b)) is administered orally to a human subject between 30 and 15 minutes prior to a meal. Claim 1 takes the format of a purpose-related product claim, pursuant to Article 54(5) EPC 2000.

Starting point in the prior art

1.3 Prior to the application, it was known that the oral delivery of calcitonin, a polypeptide hormone, may present problems, and that it may be administered together with certain delivery-enhancing agents (see D2: pages 1 and 2 and page 7, lines 25 to 34). Documents D1 and D2 are concerned with oral dosage forms containing a combination of calcitonin and delivery agents as defined in present claim 1 (in particular N-(5-chlorosalicyloyl)-8-amino caprylic acid and its (di)sodium salt), intended preferably for administration to human patients (D1: claim 1; page 5, lines 9 to 16; page 6, lines 6 to 8; page 11, lines 12 to 16; examples 2 to 5, 10 to 14; D2: claims 1 to 7; page 1, paragraph 2 to page 3, paragraph 1; page 7, lines 25 to 30; page 8, lines 26 to 28; examples).

1.4 Both documents disclose studies in which such compositions were administered to animals in fasted condition (D1: rats, D2: monkeys). They do not disclose administration at a specified time prior to a meal, or a dosage regime for human subjects.

Objective technical problem and solution

1.5 Example 7 of the present application describes a study on human subjects which was carried out with the aim of measuring the effects of administering a tablet formulation of salmon calcitonin and the disodium salt of N-(5-chlorosalicyloyl)-8-amino caprylic acid at various time intervals relative to meals. The reference condition was administration under fasting conditions. The results (mean maximum plasma concentration of calcitonin and mean AUC) are presented in table I bridging pages 12 and 13 of the description.

1.6 The appellant submitted that, according to the data in example 7, administration with a meal (treatment group F) led to only negligible plasma levels of calcitonin, and that the highest bioavailability was achieved when administering the pharmaceutical composition to a human subject between 30 and 15 minutes prior to a meal (treatment groups C and D).

1.7 Considering the data presented in example 7, it would appear that administering the tablets with a meal resulted in the lowest bioavailability of calcitonin. That option does not however represent the state of the art as set out in D1 or D2, which both disclose administration (to animals) in fasted state, and without food intake.

The test results presented in example 7 (table I) show considerable variation, as indicated by the large standard deviations. It has not been established that the differences between treatment groups C and D (administration at 30 or 15 minutes pre-meal, respectively) and treatment groups A, B, E and G (administration after overnight fast, 1 hour or

5 minutes pre-meal and 2.5 hours post-meal) are in fact statistically significant.

The board proceeds however on the assumption, made in the appellant's favour, that administration from 30 to 15 minutes prior to a meal is the dosing option which is most favourable for enhancing calcitonin bioavailability, and that the same effect of enhanced bioavailability is obtained during said time period with the alternative delivery agents mentioned in claim 1.

Thus the technical problem to be solved when starting from the technical teaching of document D1 or D2 is to identify measures by which the bioavailability of calcitonin, when administered orally in a composition together with a suitable delivery agent, reaches an optimal value.

Obviousness of the solution

1.8 Faced with that technical problem, the person skilled in the art would, as a matter of routine, consider optimising the composition, the dosage form or the dosage regime.

1.9 The appellant contended that the technical solution of applying a dosage regime which requires oral administration to a human subject from 30 to 15 minutes prior to a meal would not have been obvious to a person skilled in the art, for the reasons mentioned above (see point VII).

1.10 It is common general knowledge that food intake may affect the uptake of a drug. This was not contested by the appellant. Depending on the desired rate of uptake and drug bioavailability, patients may thus be advised to take their medication before, during or after a

meal. Hence it would have been obvious to the person skilled in the art to check any new medicament for such food effects. A systematic investigation of these effects was therefore an obvious routine measure for finding out how to optimise the bioavailability of calcitonin when administering the compositions known from D1 or D2. Based on the results of such an investigation, the person skilled in the art would then have been able, without the exercise of inventive skill, to establish a dosage regime as defined in claim 1.

1.11 For the board to decline to acknowledge inventive step in the present context, specific dosage recommendations (pointing to a time interval of 30 to 15 minutes prior to a meal) do not have to be known from the prior art as a result of previous systematic investigation. It is sufficient that it was obvious to the skilled person seeking to optimise bioavailability to carry out an investigation which was bound to provide the required information. The reason why such studies are carried out at all is that they have uncertain outcomes. But they are routine tests and the fact that their outcome is uncertain does not in itself make their results inventive.

1.12 If, as alleged by the appellant, the person skilled in the art had regarded the administration of calcitonin in the evening as preferable for maximised clinical effect, that is in any case not at odds with the requirement that the medicament be administered prior to a meal, as defined in present claim 1. Hence the appellant's argument is not relevant, since it cannot support a case of technical prejudice against the claimed subject-matter.

1.13 As a consequence of these considerations, the board has come to the conclusion that the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

2. Inventive step - auxiliary request

2.1 According to claim 1 of the auxiliary request, the disodium salt of N-(5-chlorosalicyloyl)-8-amino caprylic acid is selected as the mandatory delivery agent (component (b)). This is the delivery agent used in example 7 of the present application and which is also a preferred delivery agent in the prior art (D1 and D2, see point 1.3 above). The appellant did not rely on that particular choice of delivery agent in support of inventive step, or mention any specific technical effect associated with it. Rather, the appellant stated previously that the delivery agent was restricted to the agent literally disclosed in example 7, but that the limitation did not seem necessary, since the nature of the delivery agent was not critical for the invention (see the appellant's letter of 2 October 2013, page 2, point 2.2). Thus the limitation regarding the mandatory delivery agent does not change the assessment of inventive step presented above.

2.2 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, for the same reasons as explained in section 1 above in the context of the main request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated