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**Datasheet for the decision  
of 16 July 2019**

**Case Number:** T 0028/15 - 3.3.04

**Application Number:** 04741224.2

**Publication Number:** 1651249

**IPC:** A61K38/23, A61K9/20, A61K47/16,  
A61P19/08

**Language of the proceedings:** EN

**Title of invention:**  
Use Of Calcitonin In Osteoarthritis

**Patent Proprietor:**  
Novartis AG  
Novartis Pharma GmbH  
Nordic Bioscience A/S

**Opponent:**  
Bone Medical Limited

**Headword:**  
Calcitonin/NOVARTIS

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
Main and auxiliary requests - Inventive step - (no)

**Decisions cited:**

**Catchword:**



**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 0028/15 - 3.3.04

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.04**  
**of 16 July 2019**

**Appellant:**

(Patent Proprietor 1)

Novartis AG  
Lichtstrasse 35  
4056 Basel (CH)

(Patent Proprietor 2)

Novartis Pharma GmbH  
Brunner Strasse 59  
1230 Wien (AT)

(Patent Proprietor 3)

Nordic Bioscience A/S  
Herlev Hovedgade 207  
2730 Herlev (DK)

**Representative:**

Fabry, Bernd  
IP2 Patentanwalts GmbH  
Schlossstrasse 523  
41238 Mönchengladbach (DE)

**Respondent:**

(Opponent)

Bone Medical Limited  
c/o Ledger Corporate, Level 3,  
46 Ord Street  
West Perth, WA 6005 (AU)

**Representative:**

J A Kemp  
14 South Square  
Gray's Inn  
London WC1R 5JJ (GB)

**Decision under appeal:**

**Decision of the Opposition Division of the  
European Patent Office posted on 16 October 2014  
revoking European patent No. 1651249 pursuant to  
Article 101(3)(b) EPC.**

**Composition of the Board:**

**Chair**                    G. Alt  
**Members:**             A. Chakravarty  
                              P. de Heij

## Summary of Facts and Submissions

- I. An appeal was filed by the patent proprietors (appellant) against the decision of the opposition division to revoke European patent No. 1 651 249, entitled "*Use Of Calcitonin In Osteoarthritis*". The opponent is respondent to the appeal.
- II. The patent was opposed on the grounds of lack of novelty (Article 100(a) EPC and Article 54 EPC), lack of an inventive step (Article 100(a) EPC and Article 56 EPC), lack of sufficient disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC and Article 123(2) EPC).
- III. The opposition division considered a main and two auxiliary requests. It held, *inter alia*, that the subject-matter of claims 1 and 14 of the main request and of claims 11 to 12 of auxiliary request 1 lacked an inventive step. The opposition division did not admit auxiliary request 2 into the proceedings because the amendments it contained were held not to be occasioned by a ground of opposition (Rule 80 EPC).
- IV. The appellant submitted sets of claims of a main request and two auxiliary requests, together with the statement of grounds of appeal, all presented for the first time during appeal proceedings.
- V. The board issued a summons to oral proceedings and subsequently a communication pursuant to Article 15(1) RPBA.
- VI. Both parties informed the board in writing that they would not attend the oral proceedings.

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

VIII. Claim 1 of the main request reads:

"1. A pharmaceutical composition comprising calcitonin and an oral delivery agent for use in the treatment or/and prevention of osteoarthritis in a human patient in need thereof, wherein

(i) the calcitonin is delivered orally, and

(ii) said oral delivery agent is 5-CNAC".

Claim 1 of auxiliary request 1 reads:

"1. A pharmaceutical composition comprising calcitonin and an oral delivery agent for use in the treatment or/and prevention of osteoarthritis in a human patient in need thereof, wherein

(i) the calcitonin is salmon calcitonin and is delivered orally, and

(ii) said composition is administered to a human in an amount of 0.4 to 1 mg salmon calcitonin per day".

Claim 1 of auxiliary request 2 reads:

"1. A pharmaceutical composition comprising calcitonin and an oral delivery agent for use in the treatment or/and prevention of osteoarthritis in a human patient in need thereof, wherein

(i) the calcitonin is salmon calcitonin and is delivered orally,

(ii) said oral delivery agent is 5-CNAC, and

(iii) said composition is administered to a human in an amount of 0.4 to 1 mg salmon calcitonin per day".

IX. The following documents are referred to in this decision:

D4: Gospodinoff A. et al., Clinica Terapeutica, vol. 110, no. 2, 1984, 29-133.

D4b: translation of document D4 into English

D15: Buclin T. et al., J. Bone Miner. Res., 2002, vol. 17, 1478-1485.

D16: US 5 990 166

X. The arguments of the appellant are summarised as follows:

*Background*

Prior to the invention no orally bioavailable peptide had been approved by the FDA or the EMEA. Although attempts had been made to develop an oral formulation of calcitonin, the effect of food intake on the bioavailability and efficacy of peptide formulations had not been systematically investigated. In particular, the timing of oral calcitonin administration was completely unexplored. Since no other information on the timing of peptide drug

administration was available, the patentee had to start from scratch in order to come up with a composition with improved bioavailability and a timing regimen. Document D17 provided evidence of this.

*Inventive step - Article 56 EPC*

*Main request - claim 1*

*The problem and its solution*

Document D4 could be chosen to represent the closest prior art for the invention. It disclosed the treatment of osteoarthritis of the hip by intramuscular administration of calcitonin. It did not mention any other ways of administration and neither taught any additive to calcitonin to improve its efficacy. Thus, the difference between the disclosure in document D4 and the claimed invention were as follows: 1) omission of the oral administration of calcium, 2) replacement of intramuscular administration of calcitonin by oral administration, 3) addition of an oral delivery agent, and 4) selection of N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC) from amongst suitable oral delivery agents.

Given the above differences, the problem underlying the present invention was the provision of a composition comprising calcitonin with improved bioavailability that was more efficient in fighting osteoarthritis, in particular the simultaneous inhibition of resorption and/or normalisation of turn-over of sub-chronic bone and the stimulation of cartilage.



*Obviousness*

In considering obviousness the key question was whether a skilled person would have had a reasonable expectation of success of solving the above formulated problem by modifying the teaching in document D4. This required the person skilled in the art to make four separate decisions to take into account each of the above mentioned differences.

With regard to issue 1) above, the opposition division argued that the claims as granted did not exclude the co-administration of calcium salts. This was basically correct but was not relevant for the case. The omission of orally administered calcium salts was a distinguishing feature which the skilled person had no incentive to implement.

With regard to issue 2) above, the opposition division concluded that it would have been obvious for a skilled person to substitute the intramuscular injection of calcitonin disclosed in document D4 by oral administration as suggested in document D15. This was not correct. Document D4 suggested the intramuscular administration of calcitonin for treating coxarthrosis, while document D15 suggested the oral administration of calcitonin for bone diseases. In contrast, the present invention provided a composition for the treatment of all kinds of symptoms of osteoarthritis, in particular the simultaneous inhibition of resorption and/or normalization of turnover of sub-chronic bone and the stimulation of cartilage.

The disclosure in document D15 would not have lead the skilled person to the conclusion that oral delivery of calcitonin was not only useful for treating bone

diseases, but also for curing the various symptoms of osteoarthritis all at the same time. The conclusion reached by the opposition division that document D15 suggested that osteoarthritis could be treated by orally administered calcitonin was a case of inadmissible hindsight.

Document D15 taught the addition of an oral delivery agent to improve bioavailability of calcitonin, but as it did not teach oral administration of calcitonin for fighting osteoarthritis in general, it was not relevant that it suggested this addition.

In relation to the choice of oral delivery agent, the opposition division was furthermore basically correct that document D15 included a link to document D16 which concerned oral delivery agents derived from caprylic acid. However, the skilled person faced with that document would have had to choose from 71 possible delivery agents. There was nothing in either document D15 or D16 that would have suggested 5-CNAC. A fair reading of document D16 showed that derivatives of aminocaprylic acid were less preferred, since they did not fall under general formula (I) disclosed in the document.

*Auxiliary request 1 - claim 1*

The person skilled in the art starting from the disclosure in document D4 would have had to make four separate decisions to arrive at the claimed subject-matter. These were 1) not administering calcium salts orally, 2) replacing intramuscular administration calcitonin by oral administration, 3) adding an oral delivery agent and 4) devising an appropriate dosage regimen.

There was nothing in the cited references that suggested a dosage regimen at all. Whether calcitonin should be delivered orally during the meal, before meal, or after a meal, as well as the time interval before and/or after a meal, whether it be 5 minutes or 5 hours, were totally unknown at the time the invention was made. In the absence of any information concerning the value of a specific dosage regimen with regard to bioavailability of calcitonin when administered orally, the claims were based on an inventive step.

*Auxiliary request 2 - claim 1*

The reasons given for the main request and for auxiliary request 1 applied equally to the subject-matter of this claim.

XI. The arguments of the respondent are summarised as follows.

The subject-matter of claim 1 of the main request lacked an inventive step over the disclosure in document D4 in view of that in document D15, essentially for the reasons set out in section 3.2 of the decision under appeal. Claim 1 of the main request differed from claim 1 of the main request in the limitation that the oral delivery agent is 5-CNAC. However, that choice was not an inventive one.

Document D15 stated that the delivery agent used in its trial was a caprylic acid derivative as disclosed in document D16 (see abstract and page 1479, column 2, central paragraph) and also that it was an N-acylated amino acid (page 1479, column 1, central paragraph). Document D16 disclosed 193 individual compounds as delivery agents, and 5-CNAC was compound 109. However,

5-CNAC was the only caprylic acid derivative which appeared in all four of the preferred lists of compounds (see column 60, lines 61 to 62; column 72, lines 59 to 60; column 74, lines 3 to 4; and column 76, lines 12 to 14). A skilled person seeking to put the teaching of document D15 into effect would thus inevitably have used 5-CNAC as the oral delivery agent.

*Auxiliary request 1 - claim 1*

The considerations relating to the main request applied correspondingly to claim 1 of auxiliary request 1. The only difference was the use of a particular dosage regimen, namely 0.4 to 1 mg of salmon calcitonin (SCT) per day (instead of requiring the use of 5-CNAC as the oral delivery agent). However, document D15 disclosed the administration of SCT at doses of 0.4 or 0.8 mg within a 24 hour period (see e.g. Figure 2 on page 1481). The appellant's discussion of the influence of food intake on the bioavailability and pharmacodynamics effects of SCT was not relevant since the claimed subject-matter was not limited to the administration of SCT by reference to the timing of food intake.

*Auxiliary Request 2 - claim 1*

Claim 1 of this request simply combined the features of the claim 1 of the main and auxiliary request 1. The reasoning given for these requests applied correspondingly.

- XII. The appellant requested that the opposition division's decision to revoke the patent be set aside and that a patent be maintained on the basis of the set of claims of the main request, or alternatively on the basis of

the set of claims of auxiliary request 1 or auxiliary request 2.

XIII. The respondent requested that the appellant's appeal be dismissed.

### **Reasons for the Decision**

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

#### *Main request - claim 1*

2. The subject-matter of the claim is a purpose-limited product as provided for by Article 54(5) EPC for a second or further medical indication. The product is a pharmaceutical composition comprising calcitonin and N-(5-chlorosalicyloyl)-8-aminocaprylic acid (5-CNAC; an oral delivery agent). The therapeutic purpose is the treatment or/and prevention of osteoarthritis in a human patient and the route of administration is oral delivery.

3. The claim differs from claim 1 as granted (the main request considered by the opposition division) in that it specifies that the oral delivery agent is 5-CNAC, whereas the claim as granted only mentioned oral delivery agents as a functionally defined class. 5-CNAC was one of the agents mentioned in claim 4 as granted.

*Inventive step - Article 56 EPC*

4. Both parties and the opposition division considered that document D4 could represent the closest prior art for the claimed invention. The board sees no reason to differ. The board will also refer to document D4b, a translation of document D4 into English. The accuracy of the translation was not disputed.
5. It is common ground that document D4 discloses the use of calcitonin for the treatment of coxarthrosis, being osteoarthritis of the hip (cf. statement of grounds of appeal, point 7.1) where the calcitonin is administered by intramuscular injection, together with orally administered calcium salts (see document D4b, page 1, final paragraph).
6. Since coxarthrosis is an embodiment of the broader term osteoarthritis, the claimed subject-matter differs from that disclosed in document D4 in the route of administration, that is orally as opposed to by intramuscular injection, and in the addition of the oral delivery agent, 5-CNAC.
7. The absence of oral administration of calcium salts is not a distinguishing feature, contrary to view put forward by the appellant, as the claim does not exclude that the treatment involves oral administration of calcium salts as part of the same pharmaceutical composition or administered as a separate pharmaceutical composition together with the claimed pharmaceutical composition.
8. The technical effect of the differences defined above is to allow the oral delivery of calcitonin for treating osteoarthritis.

9. The appellant argued that the claimed invention had the effects of improved bioavailability, more efficient treatment of osteoarthritis, in particular the simultaneous inhibition of resorption and/or normalisation of turn-over of sub-chronic bone and the stimulation of cartilage. However, the board has seen no evidence that the treatment carried out as claimed is improved as compared to the treatment disclosed in document D4. The above effects are therefore not taken into account in formulating the technical problem.
10. Taking the differences defined above and the technical effect thereof into account, the problem to be solved can be formulated as the provision of a calcitonin composition that can be delivered in a convenient, easy and generally painless way (see paragraph [0003] of the patent).
11. The person skilled in the art, starting from the treatment of osteoarthritis of the hip by intramuscular injection of calcitonin disclosed in document D4 and faced with the above formulated problem, would be aware of document D15 which comes from the same general field as the invention, namely the treatment of bone diseases with calcitonin.
12. Document D15 discloses that the oral delivery of salmon calcitonin is feasible with reproducible absorption and systemic biological efficacy. It is further disclosed that an oral formulation could facilitate the use of salmon calcitonin in the treatment of osteoporosis and other bone diseases (see abstract). The oral delivery disclosed in document D15 is facilitated by use of a low molecular weight carrier derived from an N-acylated amino acid which promotes the systemic absorption of

the orally administered salmon calcitonin (see page 1479, left-hand column, paragraph 2).

13. Thus, the skilled person starting from document D4 would learn from document D15 that salmon calcitonin could be effectively orally administered together with a low molecular weight N-acylated amino acid delivery agent. In the choice of the particular carrier N-acylated amino acid to be used, reference is made to reference 27 (document D16 in the present proceedings). As noted in the decision under appeal, this document relates to oral delivery agents and provides the chemical formulae of 193 individual such agents all of which are said to be functionally effective (see column 2, lines 39 to 43) and discloses 5-CNAC as compound 109 (see column 33). This compound is one of the particularly preferred compounds (see column 60, lines 61 to 62).
14. Thus the person skilled in the art, knowing from document D4 that calcitonin was suitable for the treatment of coxarthrosis and seeking a less onerous route of administration would, in the light of the teaching in D15, have administered the calcitonin orally in combination with any of the agents disclosed in document D16.
15. The selection of a particular oral delivery agent from the general class mentioned in document D15 would also have been obvious in view of the teaching in document D16. The skilled person could and would readily have chosen any of the individual oral delivery agents disclosed in document D16 (see point 18) and would especially have selected 5-CNAC because it was mentioned as particularly preferred.



16. The appellant argued that although the disclosure in document D15 might have lead the skilled person to the conclusion that oral delivery of calcitonin was useful for treating bone diseases, it did not disclose that it was useful for treating the symptoms of osteoarthritis in general.
17. The board however is of the view that the skilled person knew from document D4 that calcitonin was useful for treating osteoarthritis of the hip. They further learned from document D15 that oral delivery of salmon calcitonin was feasible with reproducible absorption and systemic biological efficacy and they would therefore have considered that the therapeutic effect described in document D4 could be achieved also by appropriately formulated, orally delivered calcitonin.
18. In relation to the choice of an oral delivery agent, the appellant argued that there was nothing in either document D15 or document D16 to suggest the chosen agent, 5-CNAC, from amongst the many possibilities disclosed therein.
19. No argument has been made that any particular technical effect, other than effectiveness as an oral delivery agent, is associated with the choice of 5-CNAC. Thus the board must consider that 5-CNAC is merely one of the many equivalent alternatives provided by document D16. It is established case law that selecting one from a number of equally suitable solutions is considered as obvious (see Case law of the Boards of Appeal of the European Patent Office, 8th edition, I.D.9.18.7).
20. Furthermore, document D16 makes a special mention of twelve of the compounds (see column 60, lines 59 to 62) and 5-CNAC is amongst these. The board is of the view

that the skilled person seeking a particular oral delivery agents from amongst all those disclosed in document D16, would have chosen one of the compounds mentioned as particularly preferred.

21. Thus the board concludes that the subject-matter of claim 1 lacks an inventive step.

*Auxiliary request 1 - claim 1*

*Inventive step - Article 56 EPC*

22. The subject-matter of this claim differs from that of claim 1 of the main request in that the calcitonin is limited to salmon calcitonin and that no particular oral delivery agent is specified, but the dose range of calcitonin to be administered per day is stated as being in an amount of 0.4 to 1 mg.
23. As was the case for the main request, document D4 represents the closest prior art for the claimed subject-matter, which differs from that disclosed in document D4 in the route of administration, that is orally as opposed to by intramuscular injection. In addition, the pharmaceutical composition comprises an oral delivery agent and the claim specifies a particular calcitonin (salmon) and a particular dose to be used. The problem to be solved can again be formulated as the provision of a calcitonin composition that can be delivered in a convenient, easy and generally painless way.
24. The board has decided above that it was obvious for the skilled person to provide a pharmaceutical composition comprising calcitonin with an oral delivery agent for use in the treatment of osteoarthritis by oral

administration, in view of the disclosure in document D4 combined with that in document D15. It remains to be decided whether or not the skilled person would have used salmon calcitonin in an amount of 0.4 to 1 mg per day.

25. Document D15 discloses the oral administration of salmon calcitonin in doses of 400, 800 and 1200 µg within a 24 hour period (see Figure 2) for treating "*bone diseases*" (see abstract). It is disclosed that an oral formulation of salmon calcitonin associated with an acylated amino acid derivative as a carrier is able to produce all the biological effects of calcitonin in healthy volunteers. The intestinal absorption of the peptide was limited, with about 1000 µg per day by the oral route required to produce concentrations and effects equivalent to an intravenous infusion of 10 µg (see page 1482, left-hand column, "*Discussion*").
26. It is therefore apparent that the person skilled in the art, applying the teaching of document D15, would choose salmon calcitonin in a dosage of about 1000 µg per day. The person skilled in the art would therefore solve the problem with a composition that falls within the scope of the claim.
27. The appellant argued that there was nothing in the cited references that suggested a dosage regimen at all. However, as can be seen from the above reasoning, this is not a view that the board can subscribe to.
28. The appellant further argued the influence of food intake on the bioavailability and pharmacodynamics effects of salmon calcitonin was not known before the present invention. However, the board notes that the claim does not have any feature relating to the

administration of salmon calcitonin in relation to the timing of food intake and this therefore cannot play a role in the board's evaluation of inventive step.

29. The subject-matter of claim 1 is therefore regarded as obvious to the person skilled in the art starting from the disclosure in document D4 when considered in the light of that in document D15.

*Auxiliary request 2 - claim 1*

30. The subject-matter of this claim is a combination of the subject-matter of claim 1 of the main request with that of claim 1 of auxiliary request 1. It lacks an inventive step for the reasons given for the main request and for auxiliary request 1.
31. No request is allowable and therefore the appeal must be dismissed.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chair:



S. Lichtenvort

G. Alt

Decision electronically authenticated