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Bezeichnung der Erfindung: Composition for use as radiographic scanning agents
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : A61K 49/02

ENTSCHEIDUNG / DECISION
vom / of / du 11 October 1988

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent /
Titulaire du brevet : Mallinckrodt Inc.

Einsprechender / Opponent / Opposant : Commissariat à l' Energie Atomique

Stichwort / Headword / Référence : Scanning agents/Mallinckrodt

EPÜ / EPC / CBE Articles 54 and 56

Schlagwort / Keyword / Mot clé : "State of the art for the purpose of assessing inventive step"
"Inventive step (denied) - routine optimisation of required amounts of ingredients already in the state of the art"

Leitsatz / Headnote / Sommaire

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Case Number : T 250/87 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 11 October 1988

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Decision under appeal : Decision of the Opposition Division of the European Patent Office dated 12 May 1987 revoking European patent No. 0 007 676 pursuant to Article 102(1) EPC.

Composition of the Board :

Chairman : K.J.A. Jahn
Members : R.W. Andrews
G.D. Paterson

Summary of Facts and Submissions

I. The mention of the grant of European patent No. 0 007 676 in respect of patent application No. 79 200 413.7, filed 19 July 1979 and claiming priority of 31 July 1978 from a prior application filed in the United States of America, was announced on 9 November 1983 (cf. Bulletin 83/45) on the basis of seven claims.

The patent is concerned with radiodiagnostic agents and, in particular, with providing a composition for preparing a technetium-99m bone scanning agent. The use of such a scanning agent depends upon the compounding or complexing of technetium-99m with bone mineral-seeking agents.

Claim 1 reads as follows:

"1. A composition of matter for the preparation of a technetium-based bone mineral or infarct scanning agent, comprising:

(1) from 0.1mg to 0.5mg of a water-soluble reducing agent selected from stannous chloride, sulfate, maleate, and tartrate; and

(2) from 1mg to 5mg of a methanehydroxydiphosphonate selected from methanehydroxydiphosphonic acid, and water-soluble alkali metal and ammonium salts thereof."

The patent states that methanehydroxydiphosphonate (MHDP), when used in a composition as disclosed and claimed, provides both sharp bone mineral images and excellent lesion detection (cf. column 2, lines 47 to 51).

II. A notice of opposition was filed on 1 June 1984 requesting the revocation of the patent on the grounds that its subject-matter lacked novelty and did not involve an inventive step. The opposition was supported, inter alia, by the following documents:

A US-A-3 983 227
C EP-A-0 004 684 and
D Proceedings of the First World Congress of Nuclear Medicine - September 30 - October 4 1974.

III. By a decision dated 12 May 1987 the Opposition Division revoked the European patent. Although the Opposition Division concluded that the claimed subject-matter was novel in the light of the disclosure in documents A, C and D, it was considered that the subject-matter of Claim 1 did not involve an inventive step. The Opposition Division recognised that documents A and C disclosed in general terms the use of a great number of phosphonates together with pharmaceutically acceptable stannous, chromous or ferrous salts in compositions of the type presently claimed, MHDP being specifically mentioned; and that they contained worked examples using particular amounts of phosphonates other than MHDP, namely methanediphosphonate (MDP) and ethane-1-hydroxy-1,1-diphosphonate (EHDP or HEDP) in conjunction with a stannous salt. However, the Opposition Division considered that the teaching of these documents was silent as to the particular amounts of MHDP and stannous salt to be used in such compositions. As to document D, again MHDP was mentioned, but not used; the described experiment only used MDP, EHDP and a third diphosphate, aminoethyldiphosphonate (AEDP). The Opposition Division was further of the opinion that MHDP and its water-soluble alkali metal and ammonium salts were superior to the closest prior art compounds, MDP and EHDP, insofar as their use resulted in a shorter period of time between

the injection of the technetium containing composition and the beginning of skeletal imaging and that the technical problem of providing a suitable composition for improved skeleton imaging had been solved. However, in the Opposition Division's view the technical problem underlying the disputed patent in the light of the closest prior art as represented by document A was to be seen in determining the appropriate amounts of MHDP and stannous chloride, sulphate, maleate or tartrate for use in the preparation of technetium-based bone mineral or infarct scanning agents. The Opposition Division concluded that the proposed solution was obvious in the light of the cited prior art.

IV. An appeal was lodged against this decision on 13 July 1987 with payment of the prescribed fee. A statement of grounds of appeal was filed on 11 September 1987.

In this statement, the Appellant contended that a study of the relevant prior art demonstrated that there was a technical prejudice against the use of MHDP for the preparation of technetium-based bone mineral and infarct scanning agents, in particular, because this compound had not been tested by one of the leading workers in this field.

V. In his reply the Respondent maintained his view that the claimed subject-matter lacked novelty in the light of the disclosure in document D. The Respondent also argued that the technical problem was to be seen in determining the dosage of MHDP and reducing agent to be used in compositions for the stated use and that the proposed solution to this technical problem was obvious in the light of the cited prior art. Finally, there was nothing in document D which could be construed as constituting a technical prejudice against considering MHDP as a carrier for technetium.

VI. Oral proceedings, to which the Respondent was summoned, but at which he was not represented, were held on 11 October 1988. At the hearing the Board expressed its doubts as to whether the subject-matter of Claim 1 was novel in the light of the disclosure in documents A and C, particularly having regard to the fact that MHDP was specifically disclosed in these documents as a suitable "operable polyphosphonate" as an alternative to the diphosphonates (MDP and EHDP) used in the "kits" described by way of example.

The Appellant admitted that MHDP was specifically mentioned in document A but argued that there was no specific disclosure of the use of MHDP in a composition with a stannous salt for the purpose of Article 54(2) EPC, because MHDP was lost amongst the numerous other compounds which were also mentioned in document A. The use of MHDP could not therefore be clearly and unambiguously derived from the disclosure of document A. Furthermore, there was also no specific disclosure for the purpose of Article 54(2) EPC of the specific amounts of those ingredients which were required in the claims of the disputed patent. In relation to the question of inventive step since MHDP did not stand out from these other compounds it would be no more obvious to select MHDP than any of the other listed compounds and no significance could be attached to its having been mentioned. Moreover, although the weight ratios of diphosphonate carrier to reducing agent calculated from amounts of these components specified in Claim 1 of the disputed patent fell within those disclosed in document A, the compositions of Claim 1 were defined in terms of the amount of the carrier and reducing agent present in them, and the amount of 1 to 5mg for MHDP could not be clearly and unambiguously derived from the disclosure of document A.

The Appellant further contended that, starting from document A, two steps are necessary to arrive at the claimed subject-matter, viz the selection of MHDP and the determination of the amount of MHDP to be used in the composition. In his submission, the selection of one compound from a long list of compounds is to be considered as equivalent to the selection of a compound from a class of compounds defined by means of a general formula and, therefore, the criteria used for the examination of selection inventions should also be applied in the present case. Thus, although the skilled person could have selected MHDP from the list of compounds in document A, he would not have done so with the expectation of obtaining compositions with advantageous properties compared with MDP, in view of the fact that, at the priority date of the disputed patent, an acknowledged expert in the field considered that this latter compound as a carrier for Tc-99m was superior to all the other carriers he had studied so far and was the carrier of choice for bone imaging in nuclear medicine.

VII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained in unamended form. Alternatively, as an auxiliary request, he requested that the patent be maintained in amended form on the basis of a combination of Claims 1 and 5. The Respondent requested that the appeal be dismissed.

VIII. At the conclusion of the oral proceedings, the decision was announced that the appeal is dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

Main request

2. The patent in suit claims, in accordance with the main request, a composition for the preparation of a technetium-based bone mineral or infarct scanning agent comprising 0.1 to 0.5mg of stannous chloride, sulphate, maleate or tartrate and 1 to 5mg of MHDP or a water-soluble alkali metal or ammonium salt thereof.

2.1 Document C, which forms part of the state of the art pursuant to Articles 54(3) and (4) EPC for all designated Contracting States, discloses a composition, useful in the preparation of technetium-99m-based radiographic scanning agents, comprising a pertechnetate reducing agent, an organophosphonate and a stabilising amount of gentisic acid or a soluble pharmaceutically-acceptable salt or ester thereof (cf. Claims 1 and 5). The disclosure of this document with respect to the reducing agents and organo-phosphates is practically identical to that of document A (cf. page 11, lines 8 to 16, page 13, lines 18 to 29, page 18, line 3 to page 26, line 6; MHDP being specifically mentioned on page 18, lines 29 to 30 and page 20, lines 12 to 17).

Having regard to the Board's findings set out below on the basis of document A, there is no need to consider the disclosure of document C separately.

2.2 In the Table on page 966 of document D there are shown the formulae of the sodium salts of the only five 1,1-diphosphonic acids referred to in Table 1 on page 186 of the earlier article by Russell et al. (cf. Calcified Tissue Research, Volume 6, pages 183 to 196, 1970). This paper is not directed toward the use of diphosphonates in bone

scanning agents, and the results of the tests carried out by Russell et al. would not be predictive of the relative value of the tested compounds in bone scanning agents. In the paragraph headed "Materials and Methods" on page 965, document D discloses that EHDP, MDP and aminoethane-1,1-diphosphonic acid (AEDP) in the form of their sodium salts were used to prepare compositions in freeze-dried kit forms which are suitable for labelling Tc-99m. The freeze-dried compositions contain 5mg of diphosphonate and 0.25mg of the dihydrate of stannous chloride (not 0.125mg as reported in the article). In the Board's judgement the sentence "The following procedure is applicable to all the diphosphonates" in the 6th and 7th lines of the above-mentioned paragraph is to be understood as referring to the three diphosphonates in the first and second lines of this paragraph. Therefore, the teaching of this document only extends to compositions containing EHDP, MDP and AEDP and does not destroy the novelty of the subject-matter of Claim 1 in accordance with the main request.

3. Document A discloses a composition for the preparation of bone scanning agents comprising certain phosphonic acids or their pharmaceutically-acceptable salts and pharmaceutically-acceptable stannous, ferrous or chromous salts (cf. column 2, lines 37 to 47). Suitably, the compositions are contained in vials which, upon the addition of a pertechnetate solution, form very effective bone scanning agents (cf. column 2, lines 50 to 59). Operable mono-, di- and polyphosphonates for use in these compositions are defined by Formulae I to X (cf. column 2, line 66 to column 4, line 33) and specific compounds falling with those formulae, together with an indication of methods for their preparation, are disclosed in column 3, line 34 to column 8, line 11. MHDP is specifically mentioned in column 4, lines 63 and 64 as "Among the operable polyphosphonates" encompassed by Formula II, and a

method of preparing it is specifically referred to at column 5, lines 41 to 46.

Although MHDP is not given any special prominence amongst the compounds disclosed in document A, nevertheless, in the Board's judgement, document A clearly teaches that MHDP and its pharmaceutically-acceptable salts are suitable ingredients in compositions used to prepare bone scanning agents.

In order to reduce the pertechnetate solution and complex the resulting technetium-99m, a stannous, ferrous or chromous salt is used in the compositions (cf. column 8, lines 29 to 33). Especially preferred reducing and complexing salts are the chlorides and sulphates, in particular stannous chloride or sulphate (cf. column 8, lines 51 to 52 and column 9, line 10 and lines 26 to 28). Due to the ideal reduction potential of the stannous ion and the absence of absorbed water anhydrous stannous chloride is the preferred reducing agent (cf. column 9, lines 29 to 31).

For the above reasons, in the Board's judgement, amongst many other possibilities the particular combination of MHDP and stannous chloride or sulphate in a composition for the specified use had been made available to the public, for the purposes of Article 54(2) EPC, by the publication of document A. Contrary to the Appellant's submission, no specific selection of MHDP and stannous chloride or sulphate was therefore necessary.

In the Table bridging columns 9 and 10 of this prior art document there are disclosed kits in the form of glass vials containing diphosphonates, stannous chloride or chromous sulphate or mixtures thereof or ferrous sulphate, and sodium chloride or glucose. The total amounts of

diphosphate and reducing agent in these kits are 6mg and 0.16mg respectively.

In the Board's view, since Claim 1 defines a composition including specific amounts of its two specified ingredients, it should be construed as equivalent to a kit, for example in the form of a vial, containing specifically 0.1mg to 0.5mg of stannous chloride, sulphate, maleate or tartrate and 1 to 5mg of MHDP or water-soluble alkali metal or ammonium salts thereof.

Document A states at column 9, lines 4 to 10 that "a highly effective and specific bone scanning agent is prepared ... using a mixture of reducing and complexing salt ... and a phosphonate of the above enumerated group". As previously mentioned, MHDP is specifically mentioned as being within such a group. At column 10, lines 4 to 9 it is also stated that "The above components are thoroughly mixed (e.g. in the compositions hereinafter described) and packaged ... in standard glass vials of about 5ml capacity". Examples of suitable kits are glass vials containing compositions as set out in the Table bridging columns 9 and 10. At column 10, lines 36 to 39 it is stated that "Kits can, of course, contain multiples of fractions of the above amounts ...".

In the Board's view, therefore, the only possible distinction between Claim 1 and the disclosure of document A lies in the specific amounts of MHDP and reducing agent. It is not necessary to decide whether document A deprives Claim 1 of novelty, however, having regard to the Board's views as to lack of inventive step set out hereafter.

4. In the Board's opinion the closest prior art is represented by document A. In order to objectively determine the technical problem underlying the patent in suit having regard to this document, it is necessary to decide what is

actually disclosed in it in the form of a technical teaching. This teaching is not confined to the detailed information in the Examples but also embraces any information in the general description and the claims.

Although the Examples in document A do not illustrate compositions containing MHDP and stannous chloride or sulphate, in the Board's judgement, as discussed in paragraph 3 above, a true reading of this document makes such compositions available to the skilled person, and, therefore, part of the state of the art for the purpose of assessing inventive step under Article 56 EPC. Therefore, the technical problem underlying the disputed patent in the light of this technical teaching may be seen in the optimisation of compositions comprising MHDP or its pharmaceutically-acceptable salts and stannous salts with respect to the amount of these ingredients for the proposed use for the preparation of technetium-based bone scanning agents.

According to the patent in suit, this technical problem is solved by providing compositions comprising 1 to 5mg of MHDP or alkali metal or ammonium salts thereof and 0.1 to 0.5mg of stannous chloride, sulphate, maleate or tartrate.

There is no reason to doubt that this technical problem is plausibly solved by the compositions defined in Claim 1 in accordance with the main request.

4.2 However, the routine experimentation to optimise the required amounts of ingredients of known compositions for a known use falls within the normal capacity of the average skilled person. The Board would agree that such optimisation would potentially involve much work in a field such as the present patent. Moreover, the Board would accept that, on the basis of the evidence in the case, the

claimed composition provides definite benefits when compared to compositions containing diphosphonates other than MHDP. However, when considering the question of inventive step such a comparison with disphosphonates other than MHDP is not appropriate. In the Board's judgement the optimisation, which is reflected in the claimed subject-matter, should properly be regarded as an optimisation in respect of amounts only over the disclosure in document A of the use of amounts of MHDP and a stannous salt which are both of the same order of magnitude. Clearly, (as was accepted by the Appellant at the oral hearing), no new or surprising effect would be achieved by the claimed amounts of these ingredients, when compared with the amounts of these ingredients disclosed in document A as discussed in paragraph 3 above. Therefore, the subject-matter of Claim 1 in accordance with the main request does not involve an inventive step.

4.2 Claims 2 to 6, which relate to preferred embodiments of Claim 1, do not contain any independent features and are, therefore, unpatentable in the absence of an allowable main claim.

The subject-matter of Claim 7, which relates to a composition as defined in Claims 1 to 6 in combination with radioactive technetium, also does not involve an inventive step, since it is known from document A to prepare bone scanning agents by combining MHDP and stannous salts with radioactive technetium in the form of pertechnetate-99m (cf. column 9, lines 4 to 10 in combination with column 4, lines 63 and 64 and column 9, lines 26 to 31).

Auxiliary request

5. Claim 1 in accordance with the auxiliary request differs from that of the main request insofar as it contains the

additional feature that the weight ratio of MHDP or a water-soluble alkali metal or ammonium salt thereof to the reducing agent selected from stannous chloride, sulphate, maleate and tartrate is in the range of from 8:1 to 13:1. There is no objection to this claim under Article 123 EPC.

5.1 As compared to the disclosure of documents A, C and D, the subject-matter of the main claim in accordance with the auxiliary request is considered to be novel in the absence of any disclosure of weight ratios falling with the specified range (cf. document A, exemplified 37.5:1, or generally a molar ratio of phosphonate to stannous ion of 15:1 to 80:1 in column 9, lines 59 to 61; document C, exemplified 36.9:1, or generally a range of 20:1 to 50:1 on page 33, lines 1 to 5; document D, 20:1 in the 4th and 5th lines of the paragraph headed "Materials and Method").

5.2 In the light of the disclosure of document A the technical problem underlying the patent in suit in accordance with the Appellant's auxiliary request may be again seen in the optimisation of the compositions containing MHDP and stannous ions with respect to their use for the preparation of bone scanning agents. For the reasons given in paragraph 4.1 above, the subject-matter of the main claim in accordance with the auxiliary request does not involve an inventive step.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S.Fabiani K.Jahn

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