BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

Datasheet for the decision of 10 January 2013

Case Number: T 2144/08 - 3.3.02

Application Number: 03013794.7

Publication Number: 1350524

IPC: A61K 49/06, A61K 49/18

Language of the proceedings: EN

Title of invention:
A MRI contrast medium composition

Applicant:
CMC Contact AB

Opponent:
-

Headword:
A MRI contrast medium composition/CMC contrast AB

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (yes): improved effect"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 2144/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 10 January 2013

Appellant: (Applicant)
CMC Contrast AB
C/o Öresund Healthcare Management AS
Ideon
S-223 70 Lund (SE)

Representative:
Presland, Torbjörn
Awapatent AB
P.O. Box 45086
S-104 30 Stockholm (SE)

Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 6 June 2008 refusing European patent application No. 03013794.7 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: D. Boulois
L. Bühler

Summary of Facts and Submissions

I. European patent application No. 03 013 794.7 was refused by a decision of the examining division, pronounced during oral proceedings held on 21 November 2007, on the grounds of non-compliance with Articles 54 and 56 EPC.

II. The decision was based on the main request submitted with the letter dated 4 July 2005 and the auxiliary request submitted with the letter dated 27 February 2006.

Independent claim 1 of the main request read:
"1. A MRI contrast medium composition for oral administration for examination of the liver, comprising as an active ingredient a physiologically acceptable manganese (II) compound, and for enhancing the uptake of manganese one or more physiologically acceptable amino acids and optionally one or more subtypes of vitamin D, wherein the manganese compound and one or more physiologically acceptable amino acids and optionally one or more subtypes of vitamin D are in a combination stimulating and providing an active transport over the intestinal wall and in an amount necessary for obtaining a high concentration in the liver for allowing a diagnostic image thereof."

Independent claim 1 of the auxiliary request read:
"1. Use of a physiologically acceptable manganese (II) compound as an active ingredient, and, for enhancing the uptake of manganese, one or more physiologically acceptable amino acids and optionally one or more subtypes of vitamin D, for the preparation of an MRI

contrast medium composition for oral administration for examination of the liver, wherein the manganese compound and one or more physiologically acceptable amino acids and optionally one or more subtypes of vitamin D are in a combination stimulating and providing an active transport over the intestinal wall and in an amount necessary for obtaining a high concentration in the liver for allowing a diagnostic image thereof."

III. The documents cited during the examination proceedings included the following:
(2) EP-A-308 983
(6) WO87/04622

IV. In the decision under appeal, the examining division found that the main request did not meet the requirements of Article 54 EPC and that the auxiliary request did not meet the requirements of Article 56 EPC.

According to the examining division, the subject-matter of claims 1-4 of the main request was not new, since an NMR image enhancing composition comprising a Mn(II) compound and an amino-acid was known from document (2). The compositions disclosed in document (2) comprised the same components as the composition claimed in claims 1-4 of the main request.

Document (2) was seen as the closest prior art for the subject-matter of claims 1-4 of the auxiliary request. Document (2) disclosed compositions which could be administered rectally, orally or parenterally. The preferred compositions were parenteral compositions for imaging the head, heart, liver or the kidney (see

page 5, lines 7-13). The compositions of document (2) were prepared in the same way as the compositions of the present application and were therefore identical. Examples 26 and 27 disclosed the parenteral use of the compositions for imaging the liver.
The subject-matter of claims 1-4 consisted in the selection of the oral way of administration for imaging the liver. Such a selection was obvious for the skilled person, taking into account the known first passage through the liver after oral administration. Hence, the subject-matter of claims 1-4 was not inventive over document (2).

V. The applicant (appellant) filed an appeal against the first-instance decision.

VI. With its statement of grounds of appeal dated 14 October 2008, the appellant provided further arguments and requested that a patent be granted on the basis of claims 1-4, corresponding to the auxiliary request before the examining division.

VII. The board sent the appellant a communication pursuant to Article 15(1) RPBA dated 13 September 2012 as an annex to the summons to oral proceedings.

VIII. With a letter dated 7 December 2012, the appellant informed the board that it would not be represented at the oral proceedings.

IX. Oral proceedings before the board of appeal took place on 10 January 2013.

X. The appellant's arguments can be summarised as follows:

Document (2) does not make obvious to the skilled person the oral administration of its imaging composition for imaging the liver. The mention of both "oral administration" and "imaging...the liver" are isolated statements in document (2), which combination was contrary to common general knowledge at that date and appeared to be an ex post facto analysis. Furthermore, at the priority date, it was not known whether the "first pass effect" applied to manganese compounds. The statement that it was obvious that manganese underwent a first pass effect was pure hindsight.

XI. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the request filed with the statement of grounds of appeal dated 14 October 2008.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request - inventive step*

2.1 The present invention relates to magnetic resonance imaging (MRI) of the liver, obtained by the oral administration of an MRI contrast medium composition comprising manganese and an intestinal uptake promoter, namely one or more physiologically acceptable amino acids (see page 1, lines 4-6, page 4, lines 1-17 and examples A and B of the application).

2.2 Document (2), which constitutes the closest prior art, is concerned with the use of manganese coordination complexes in magnetic resonance imaging (see page 2, lines 2-5). The compositions of document (2) are based on the discovery that non-chelate coordination complexes of amino-acids with Mn^{2+} substantially reduce toxicity without the reduction in relaxivity experienced with chelates (see page 3, lines 10-12). The compositions may be administered rectally, orally or parenterally (page 5, line 9). Oral administration is not disclosed directly and unambiguously for imaging the liver and the preferred compositions are designed for parenteral administration for imaging the head, heart, liver and kidney (see page 3, lines 40-50; page 4, lines 54-57; page 5, lines 7-13; examples 22, 26-29).

2.3 The problem underlying the present invention may be seen as the provision of an enhancement of the MRI imaging of the liver.

The proposed solution to this problem is the use of an MRI contrast medium composition comprising manganese and an uptake promoter, namely one or more physiologically acceptable amino acids, characterised by its oral administration.

The absorption of manganese through the gut is indeed poor, and may be enhanced by uptake promoters such as amino acids. The increase in the intestinal uptake of manganese is demonstrated by examples A and B and figures 1-3 of the application (see page 5, line 16-page 6, line 6, figures and examples).

Moreover, the oral ingestion exposes only the enterohepatic circulation. The absorption of manganese through the intestinal wall and the portal vein circulation delivers the manganese solely to the hepatocytes and the manganese is completely absorbed by the hepatocytes on its first passage through the liver because of its strong affinity. The portal delivery of manganese and the further first-pass effect will thus be able to give a maximal differentiation between healthy and pathological tissues.

On the other hand, parenterally administered manganese will expose all organs of the body, and will reach the liver through the arterial blood supply. Tumours, which require a large supply of oxygen, get their main supply from the arterial circulation which provides oxygen-rich blood, and will be fed by the parenterally circulating manganese. Parenteral manganese will thus give considerably less differentiation between tumorous and healthy liver tissues, and therefore less probability of detecting a tumour in the liver.

Thus, by oral administration and the further portal delivery of manganese, it is possible to avoid systemic exposure and consequent possible adverse effects on other organs and to maximise the delivery to the liver cells, in order to give maximal differentiation between healthy and tumorous liver tissues.

The association of the oral mode of administration with the imaging of the liver gives rise to an unexpected technical effect, namely an intestinal uptake enhancement of manganese and a liver imaging enhancement.

The examples of the description establish the credibility of the presence of an improvement vis-à-vis the closest state of the art. The board is thus convinced that the above problem has been plausibly solved.

2.4 Thus, the question to be answered is whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

Document (2) does not suggest that the oral mode of administration may be used for imaging the liver, and specifies rather that the mode of administration is selected to provide an RMI image of the portion of the body to be imaged.

The intestinal uptake enhancement, the consequent first pass effect of manganese and the liver imaging enhancement are also known neither from document (2), nor from any other document cited during the examination proceedings or from common general knowledge. All these effects are unexpected.

Document (6) discloses that chelates of amino acids and manganese may selectively target the liver through an oral administration (see page 5, lines 8-13; page 12; page 15, lines 5-6). The teaching of document (6) relates however to a particular form of complexes, namely chelates, which are explicitly excluded by the teaching of the closest prior-art document (2), and does not mention any uptake enhancement. The association of the teaching of this document with that of document (2) is not possible.

The other documents cited during the proceedings are more remote than documents (2) or (6).

The use of the oral way of administration for obtaining an enhanced MRI imaging of the liver by a composition comprising manganese and amino acids is therefore not obvious.

2.5 The requirements of Article 56 EPC are therefore met for the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent with the following claims and a description to be adapted thereto:
Claims: No 1-4 filed with the statement of grounds of appeal dated 14 October 2008.

The Registrar: The Chairman:

N. Maslin U. Oswald