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Datasheet for the decision of 31 July 2008

Case Number: T 0077/06 - 3.3.02

Application Number: 00936887.9

Publication Number: 1191949

IPC: A61K 51/12

Language of the proceedings: EN

Title of invention:
Stent for neutron capture therapy and method of manufacture therefor

Applicant:
Abbott Laboratories Vascular Enterprises Limited

Headword:
Stent for neutron capture therapy/ABBOTT LABORATORIES VASCULAR ENTERPRISES LIMITED

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"All requests: Inventive step (no): selection of stents comprising an element having a high neutron capture cross-section for preventing restenosis is obvious"

Decisions cited:
-

Catchword:
-

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Case Number: T 0077/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 31 July 2008

Appellant: Abbott Laboratories Vascular Enterprises Limited
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 29 August 2005 refusing European application No. 00936887.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
J. Van Moer

Summary of Facts and Submissions

I. European patent application No. 00 936 887.9 (publication No. WO 00/76557) was refused by a decision of the examining division of 29 August 2005 on the basis of Article 97 EPC on the grounds of lack of inventive step under Article 56 EPC.

II. The following documents were *inter alia* cited during the proceedings before the examining division and the board of appeal:

(1) J.-L.A. Shih and R.M. Brugger: "Neutron induced brachytherapy: A combination of neutron capture therapy and brachytherapy" Medical Physics, vol. 19, no. 2, March/April 1992, pages 369-375
(2) EP-A-0 857 470
(3) US-A-5 840 009
(4) US-A-5 947 889
(4a) DE-A-196 00 669

III. The decision was based on claims 1-19 of the main request filed with letter dated 15 January 2002 (entry into the European phase).

Independent claims 1 of the main request before the examining division read as follows:

"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns.

15. A method of manufacturing a stent for neutron capture therapy, the method comprising introducing a material into a body portion of the stent, the material incorporating a stable atomic element having a neutron capture cross-section greater than 1000 barns."

IV. The arguments in the decision may be summarised as follows:

The examining division defined document (2) as closest prior art which related to stents comprising radionuclides emitting radiation with a defined half life rather than stable atomic elements having a neutron capture cross-section greater than 10^3. The provision of alternative, eventually improved stents was then defined as the objective problem. The solution in the form of a stent according to claim 1 was obvious, as the person skilled in the art knew from document (2) that γ-radiation emitting radionuclides such as tantalum, activated by a neutron flux, could be used in stents. The person skilled in the art, looking for alternatives, would take into consideration elements that emitted γ-radiation upon neutron capture and would learn from document (1) that gadolinium (Gd) had the highest neutron capture cross-section of all elements and that the emission of radiation only occurred during irradiation with neutrons. As radioactive materials were routinely used in the treatment of both cancer and restenosis, the person skilled in the art, trying to solve the problem defined above, would have taken into consideration the teaching of document (1). As a consequence, the subject-matter of claims 1 to 14 as well as of 15 to 19 lacked an inventive step.

V. The appellant (applicant) lodged an appeal against said decision.

VI. At the oral proceedings of 31 July 2008, the appellant filed auxiliary requests I to V. The respective claims 1 of each auxiliary request read as follows:

(a) auxiliary request I:
"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that emits therapeutic radiation, characterized in that the material incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns and emits therapeutic radiation substantially only while being exposed to a thermal neutron irradiation."

(b) auxiliary request II:
"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that emits therapeutic radiation, characterized in that the material incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns and emits therapeutic radiation with a half-life on the order of less than several milliseconds."

(c) auxiliary request III:
"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns, characterized in that the stable atomic element is ^{157}Gd."

(d) auxiliary request IV:
"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns, characterized in that the material incorporates a stable atomic element selected from ^{149}Sm, ^{113}Cd and ^{151}Eu."

(e) auxiliary request V:
"1. A stent for neutron capture therapy, the stent comprising a body portion fabricated from a material that incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns, characterized in that the stable atomic element is ^{149}Sm."

VII. The appellant's submissions can essentially be summarised as follows:

The problem of the present invention concerned the provision of a stent for neutron capture therapy, where restenosis of cells of the vessel walls adjacent to its ends was inhibited and which also allowed a temporal separation between placement of the stent and irradiation as well as repetition of the radiation therapy as needed. This problem was solved by a stent incorporating a stable atomic element having a neutron capture cross-section greater than 1000 barns. Document (2), which related to stents comprising an element such as tantalum (Ta) or iridium (Ir), which were rendered radioactive by exposure to a neutron flux in a conventional fission reactor and then continuously released low-dose ß-radiation over a prolonged period

of time, was defined as closest prior art. The provision of alternative stents for the treatment or prevention of restenosis was defined as the objective problem with regard to this prior art.

The skilled person had no reason to change from ß-radiation, which was considered the most effective and appropriate radiation for treating restenosis, to γ-radiation, which was used in document (1). On the contrary, the state of the art gave a clear preference to ß-radiation, which was also the method of choice in document (2). Secondly, the person skilled in the art would have to change from a static constant radiation source to short-term radiation bursts triggered by external irradiation, which had only been used in connection with cancer therapy. Thirdly, even if the skilled person had envisaged such a change, he still would have had to select the right material, which, as was mentioned above, was only disclosed in connection with cancer therapy.

When trying to solve the problem of restenosis in connection with stents, the person skilled in the art would for various reasons not turn to a document dealing with the treatment of cancer. To begin with, there was an important difference in size: in cancer treatment, the tissue to be irradiated had an expansion of from about 1 to 10 cm; treatment of restenosis on the other hand involved the selective irradiation of the very thin neointima, where the short-range ß-radiation was clearly preferable to the long-range γ-radiation. Secondly, severe side-effects, which were tolerable in cancer treatment, were unacceptable in the treatment of restenosis.

Moreover, the present invention comprised additional beneficial effects: there was no health risk for the doctor, as the stent was introduced into the body in a non-radioactive state, the position of the stent could be verified before the start of the treatment and the radiation could be controlled so that it was possible to apply it only when needed.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 14 as published and 15 to 19 filed on January 15, 2002 as a main request or, in the alternative on the basis of auxiliary requests I to V filed during the oral proceedings.

Reasons for the decision

1. The appeal is admissible.

2. With his letter dated 17 July 2008 the appellant submitted document (4) as "English translation" of the German family member (document (4a)). In view of the fact that document (4) was published after the priority date of the application under appeal, the board will subsequently refer to the pre-published document (4a).

3. Inventive step:

3.1. Main request:

3.1.1. The application under appeal concerns stents for neutron capture therapy comprising a stable atomic

element that may be externally activated by thermal neutrons, thereby providing localised neutron capture therapy in the vicinity of the vessel around the stent for reducing restenosis (see page 1, lines 4-10 and page 6, lines 7-11 of the original application).

3.1.2. Document (2) is also concerned with stents comprising an element that emits radiation in order to reduce or prevent restenosis. The ß-emitting Ta^{182} and Ir^{192} are selected as radioactive source (see column 4, lines 19-24 and 41-45). Like in the application under appeal, the stents are produced by using stable elements that are subsequently activated by a neutron flux. According to the teaching of document (2), the activation is carried out before the stents are placed into the body (see column 3, lines 39-43). In view of the fact that it teaches activation of stable elements via a neutron flux, document (2) is considered to represent the closest prior art.

3.1.3. In the light of this prior art, the problem is defined as follows: provision of alternative stents comprising stable elements susceptible of being activated by a neutron flux for the treatment or prevention of restenosis. In this context, it is emphasised that the different time of activation via neutron flux (after introduction into the human body according to the application under appeal vs. before introduction into the human body according to document (2)) is not taken into consideration for the definition of the problem, as the method of activation is not an inherent property of the stent. Thus, it would also be possible to activate stents as disclosed in document (2) after their placement into the body of the patient. The

problem is solved by a stent that incorporates a stable atomic element having a neutron capture cross-section greater than 10^3 barns.

3.1.4. From the description, in particular from the passage on pages 6-12, the board is satisfied that the problem is plausibly solved.

3.1.5. When evaluating whether the solution to this problem, i.e. the replacement of the ß-emitting Ta^{182} and Ir^{192} of document (2) by a stable element having a neutron capture cross-section greater than 1000 barns and in particular by Gd^{157}, is obvious, it appears useful to first examine whether the person skilled in the art would take into consideration the use of stents comprising γ-emitting elements for treating restenosis at all. In this context, it is emphasised that according to the argumentation of the appellant, the elements having a neutron capture cross-section greater than 1000 barns are essentially γ-emitting elements. The board has no reason to doubt this.

The appellant correctly pointed out that the use of ß-emitting elements for treating restenosis is clearly preferred. This can be derived from document (2) (see column 1, lines 35-37 and column 4, lines 19-24) and document (3), which is also concerned with radioactive stents for minimising restenosis (see column 1, lines 24-29 and column 2, lines 64-65). Reference is also made to document (4a), which describes the preference of ß-emitting elements over γ-emitting elements for the treatment of restenosis in connection with the closely related balloon catheters (see column 1, lines 37-49 and column 2, lines 36-39). The reason for this

preference of the ß-emitting elements is also known to the skilled person: the neointima in the blood vessels are very thin. As a consequence, ß-emitters, which are mainly effective at short ranges, are advantageous for a localised treatment over γ-emitters, which penetrate into the body of the patient, as they are not completely adsorbed by the arterial wall (see column 1, lines 37-46 of document (4a)).

However, it is important to note that the person skilled in the art is aware that stents comprising γ-emitting elements, even if less preferred, can be used for treating restenosis. This is reflected in document (3) (see column 2, lines 66-67). As a consequence, the replacement of the elements disclosed by a γ-emitting substance is obvious, as long as the person skilled in the art is prepared to put up with the fact that the radiation might be less localised than the radiation with ß-radiating substances.

3.1.6. As the next step, it has to be analysed whether the person skilled in the art would have selected the elements having a neutron capture cross-section greater than 1000 barns out of the larger group of γ-emitting elements. In the light of the problem as defined above, i.e. the provision of alternative stents comprising stable elements **susceptible of being activated by a neutron flux** for the treatment or prevention of restenosis, he most certainly would have chosen these elements, as the neutron capture cross-section is a measure for the probability of neutron capture. The higher the neutron capture cross-section, the easier the activation via a neutron flux. For that reason alone, the selection of elements having a neutron

capture cross-section greater than 1000 barns such as e.g. ^{157}Gd or ^{149}Sm is obvious. ^{157}Gd is particularly preferred for having the highest neutron capture cross-section of all stable nuclides (see document (1), page 370, bottom half of the left-hand column). As a consequence, the subject-matter of claim 1 of the main request does not meet the requirements of Article 56 EPC.

3.2. Auxiliary request I:

As compared to claim 1 of the main request, the subject-matter of claim 1 additionally comprises the feature that the atomic element emits therapeutic radiation substantially only while being exposed to a thermal neutron irradiation. However, this feature is a direct consequence of a short half-life of an element such as e.g. Gd in its radioactive state. In view of the fact that the choice of an element such as ^{157}Gd was found to be obvious (see paragraphs 3.1.1 to 3.1.6 above), this additional feature is not suitable for establishing an inventive step either.

3.3. Auxiliary request II:

As compared to claim 1 of the main request, the subject-matter of claim 1 additionally comprises the feature that the atomic element emits therapeutic radiation with a half-life on the order of less than several milliseconds. However, it is general common knowledge that an element such as ^{157}Gd has such a short half-life. (see also page 11, lines 7-13 of the application as filed). In view of the fact that the choice of an element such as Gd was found to be obvious (see paragraphs 3.1.1 to 3.1.6 above), this additional

feature is not suitable for establishing an inventive step either.

3.4. Auxiliary request III:
As compared to claim 1 of the main request, the subject-matter of claim 1 additionally comprises the feature that the stable atomic element is ^{157}Gd. In view of the fact that the choice of an element such as ^{157}Gd was found to be obvious (see paragraphs 3.1.1 to 3.1.6 above), this additional feature is not suitable for establishing an inventive step either.

3.5. Auxiliary request IV:
As compared to claim 1 of the main request, the subject-matter of claim 1 additionally comprises the feature that the stable atomic element is selected from ^{149}Sm, ^{113}Cd and ^{151}Eu. In view of the fact that the selection of an element such as ^{149}Sm was found to be obvious (see paragraphs 3.1.1 to 3.1.6 above), this additional feature is not suitable for establishing an inventive step either.

3.6. Auxiliary request V:
As compared to claim 1 of the main request, the subject-matter of claim 1 additionally comprises the feature that the stable atomic element is ^{149}Sm. In view of the fact that the selection of an element such as ^{149}Sm was found to be obvious (see paragraphs 3.1.1 to 3.1.6 above), this additional feature is not suitable for establishing an inventive step either.

3.7. As a consequence, none of the requests on file meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

N. Maslin U. Oswald