Aktenzeichen / File Number / Numéro du dossier

T0233 / 96 -332

In der Anlage erhalten Sie

- ☐ eine Kopie des Berichtigungsbeschlusses
- ☐ ein korrigiertes Vorblatt (Form 3030)
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Please find enclosed

- ☐ a copy of the decision correcting errors
- ☐ a corrected covering page (Form 3030)
- ☒ Corrected a headnote / catchword (Form 3030)
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- ☐ une copie de la décision rectifiant des erreurs
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- ☐ un sommaire / une phrase vedette (Form 3030)
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Anmeldung Nr. / Patent Nr.: _____
(soweit nicht aus der Anlage ersichtlich)

Application No. / Patent No.: 89303960.2
(if not apparent from enclosure)

Demande n° / Brevet n°: _____
(si le n° n'apparaît pas sur l'annexe)

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D E C I S I O N
of 4 May 2000

Case Number: T 0233/96 - 3.3.2

Application Number: 89303960.2

Publication Number: 0354638

IPC: A61K 31/70

Language of the proceedings: EN

Title of invention:
Use of adenosine and its derivatives in diagnosis

Applicant:
MEDCO RESEARCH INC

Opponent:
-

Headword:
Adrenaline/MEDCO RESEARCH

Relevant legal provisions:
EPC Art. 56

Keyword:
"Novelty (yes): after limitation"
"Inventive step (no): claimed diagnostic application of adenosine obvious in view of its known diagnostic and therapeutic application"
"Second auxiliary request: reference to "humans who are unable to exercise adequately" no novel diagnostic application"

Decisions cited:
T 0021/81, T 0019/86, T 0893/90

Headnote:
If the use of a compound was known in the treatment or diagnosis of a disease of a particular group of subjects, the treatment or diagnosis of the same disease with the same compound could nevertheless represent a novel therapeutic or diagnostic application, provided that it is carried out on a new group of subjects which is distinguished from the former by its physiological or pathological status (T 0019/86, T 0893/90).
This does not apply, however if the group chosen overlaps with the group previously treated or the choice of the novel group is arbitrary which means that no functional relationship does exist between the particular physiological or pathological status of this group of subjects (here humans who are unable to exercise adequately) and the therapeutic or pharmacological effect achieved.

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0233/96 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 4 May 2000

Appellant: MEDCO RESEARCH INC
8733 Beverley Boulevard
Suite 404
Los Angles
California 90048 (US)

Representative: Cresswell, Thomas Anthony
J.A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX (GB)

Decision under appeal: Decision of the Examining Division of the European Patent Office posted 12 October 1995 refusing European patent application No. 89 303 960.2 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: C. Germinario
Members: C. F. E. Rampold
M. B. Günzel

Summary of Facts and Submissions

I. European patent application No. 89 303 960.2, published as EP-A-0 354 638, was refused under Article 97(1) EPC by a decision of the examining division dated 12 October 1995. That decision was based on the main request and an auxiliary request, both in the version filed on 30 January 1995.

II. In the course of the examination proceedings a third party had presented observations under Article 115 EPC, submitting that the claimed subject-matter in the application was not patentable due to lack of novelty and inventive step. In support of this submission, reference was made, *inter alia*, to the following citations:

(10) WO 87/01593 (also cited in the search report)

(11) A. Sollevi, "Cardiovascular effects of adenosine in man; possible clinical implications", published in Progress in Neurobiology, vol. 27, 1986, pages 319-349

III. The stated ground for the refusal was that the invention did not involve an inventive step (Articles 52(1), 56 EPC). The substance of the reasoning given in the decision of the examining division was as follows:

Several prior art documents cited in the course of the examining proceedings already disclosed the use of papaverine or dipyridamole as pharmacological stressors to increase the myocardial oxygen supply in patients for the assessment of the extent and severity of heart diseases in conjunction with invasive or non-invasive diagnostic techniques. It was moreover known from

citation (1), *viz.* the paper of J. A. Rumberger et al. published in J. Am. Coll. Cardiol. vol. 9 , No. 1, 1987, pages 59-69, that adenosine was already used as a coronary vasodilator in myocardial perfusion measurements in dogs and that this approach was contemplated to offer scope for the quantitative assessment of myocardial flow reserve in humans using adenosine as a pharmacological stressor. More specifically, this approach was expected in (1) to aid significantly in the diagnosis and treatment of patients with cardiovascular disease.

In the opinion of the examining division it was thus obvious to a person skilled in the art to substitute adenosine for other pharmacological stressors conventionally used in conjunction with invasive or non-invasive techniques for assessing patients with coronary artery disease, such as papaverine or dipyridamole, since the diagnostic value of this substitution was considered in (1) to be promising for the assessment of heart diseases belonging to those specifically mentioned in claim 1 of the application. In this context, the examining division pointed also to the fact that certain documents uncovered by the search report or submitted by the third party, for example citation (10), already described, before the priority date, the use of adenosine for the treatment of human patients.

As to the auxiliary request, the examining division held that, once the use of adenosine as a coronary vasodilator became obvious, determination of the optimum dosage range required to achieve the desired vasodilating effect in human patients was purely a matter of routine experimentation for the skilled practitioner.

IV. The appellant (applicant) lodged an appeal against this decision. The statement of grounds was accompanied by a revised main request, three auxiliary requests and, among other documents, the following publication:

(14) F. Zijlstra et al. "Value and Limitations of Intracoronary Adenosine for the Assessment of Coronary Flow Reserve"; published in Catherization and Cardiovascular Diagnosis 15, 1988, pages 76-80.

V. The board, in the annex to the summons to attend oral proceedings, informed the appellant that both novelty and inventive step would have to be discussed during oral proceedings on the basis of the prior art documents introduced into the proceedings.

VI. At the beginning of the oral proceedings, held on 4 May 2000, the board raised doubts as to the novelty of the main and second auxiliary requests, submitted with the appeal statement, in the light of the prior art, document (14). As a consequence of this, the appellant submitted in substitution for all previously filed requests a revised main request and two revised auxiliary requests:

Claim 1 of the main request is worded as follows:

"The use of a compound which is adenosine or a functional adenosine receptor agonist, in the preparation of a diagnostic agent for the assessment of myocardial dysfunction, of coronary artery disease, of ischemic ventricular dysfunction, or of vasadilatory capacity of coronary arteries by parenteral administration to a human of the compound in conjunction with an invasive or non-invasive technique, wherein the diagnostic agent is in unit dosage form,

comprising from 20 to 200 µg/kg/min when formulated for intravenous administration or from 2 to 20µg when formulated as a bolus for intracoronary administration"

Claim 1 of the first auxiliary request corresponds to claim 1 of the main request with the sole exception that it is restricted to the use of adenosine in the preparation of the diagnostic agent.

Claim 1 of the second auxiliary request reads as follows:

"The use of adenosine as a pharmacological stressor in the preparation of a diagnostic agent for detecting the presence, or assessing the severity, of vascular disease of coronary arteries by parenteral administration to a human who is unable to exercise adequately in conjunction with radioimaging of the coronary arteries wherein the adenosine is in unit dosage form, comprising from 20 to 200 µg/kg/min of the compound when formulated for intravenous administration or from 2 to 20 µg when formulated as a bolus for intracoronary administration."

VII. The appellant's submissions presented in writing and during oral proceedings can substantially be summarised as follows:

The problem addressed by the invention was to provide a method of diagnosing various types of heart disease in humans which was safe, effective and could be approved for routine clinical examinations by qualified physicians. Although a person skilled in the art at the priority date might have been aware that these problems existed, it would not have been apparent that all the problems could be solved simply by the use of adenosine as a vasodilator and pharmacological stressor.

The two vasodilators that were finding favour in the state of the art before the priority date were dipyridamole and papaverine. In Example I of the present application it was unexpectedly found that adenosine improved the overall sensitivity and accuracy of detection of coronary artery disease when compared with the use of dipyridamole. In Example III adenosine was compared with papaverine. It was found that adenosine, unlike papaverine did not routinely prolong the QT interval and, in addition, it was found by chance that maximal coronary hyperemia occurred sooner with adenosine than with papaverine and was resolved sooner. These benefits could not have been predicted from the art and provided evidence of inventive activity.

Moreover, document (14), which was published only shortly before the priority date, provided evidence that a prejudice existed in the state of the art against using adenosine as a pharmacological stressor to assess patients with coronary artery disease, in particular in conjunction with radioimaging.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted with the claims of the main request filed at the oral proceedings. As auxiliary requests he requested that a patent be granted with the claims of any of the first or second auxiliary requests filed at the oral proceedings, taken in their numerical order.

Reasons for the Decision

1. The appeal is admissible.

Amendments

2. The claims as amended by the appellant during the appeal proceedings are adequately supported by the originally filed documents. The present requests comply in this formal respect with the provisions of Articles 84 and 123(2) EPC.

Main and first auxiliary requests:

3. The sole difference between the main request and the first auxiliary request resides in the limitation of the definition of the compound used as the vasodilator. While that compound is broadly defined in the main request as "*adenosine or a functional adenosine receptor agonist*", its definition is limited in the first auxiliary request to "*adenosine*" as such. Since the prior art cited in this decision refers specifically to the use of adenosine, the following observations and conclusions apply in every aspect equally to the main and first auxiliary requests.

4. The invention relates to the use of adenosine or a functional adenosine receptor agonist as a vasodilator, which is used as a physiological stressor, in conjunction with any invasive or non-invasive diagnostic technique, e.g. coronary arteriography using a Doppler flow catheter, radioimaging or echocardiography, to assess patients with known or suspected coronary artery or myocardial disease (see application as filed, especially page 3, lines 7 to 17). Claim 1 according to all the main and auxiliary requests provides the intravenous administration of

adenosine (or a functional adenosine receptor agonist) in doses of from 20 to 200 μg/kg/min, or intracoronary bolus injection, in doses of from 2 to 20 μg.

4.1 The closest state of the art, *viz.* publication (14), compares the effects achieved by the intracoronary bolus injection of papaverine on the one hand and adenosine on the other as a vasodilator (physiological stressor) to patients suffering from one- or two-vessel coronary artery disease. Citation (14) is concerned, inter alia, with a method of assessment of *coronary blood flow reserve*, which is defined as the ratio of maximal coronary blood flow to resting flow, and is said to be essential in understanding the physiological significance of coronary artery obstructions. The measurements of coronary blood flow reserve were evaluated in the course of coronary arteriography using a Doppler flow catheter. The document discloses the intracoronary administration of adenosine to patients as the sole mode of administration and found that relatively large doses of adenosine, which vary from one patient to another within the broad range of from 0.05 mg (50 μg) to 0.8 mg (800 μg), were required to induce maximum hyperemic response (see page 78, Table II).

4.2 On the basis of the different regimen of administration disclosed in (14) as compared to the present invention, the subject-matter of claim 1 according to the main and first auxiliary request is regarded as novel.

5. As can be derived from the comparative tests reported in (14), both papaverine and adenosine act as potent coronary vasodilators in humans and exhibit about the same magnitude of the hyperemic response (vasodilation) after intracoronary administration. However, adenosine compares favourably with papaverine and dipyridamole as well in that it induces coronary hyperemia much more

quickly and is likewise much more rapidly cleared from the bloodstream. Moreover (14) refers at the end of the left-hand column on page 76 to the problem of papaverine possibly precipitating with certain radiographic contrast agents, thereby causing serious complications.

5.1 The passage in (14) entitled "Complications" (see the paragraph bridging the left and right-hand columns on page 78) states that in three patients intracoronary administration of adenosine resulted in bradyarrythmias, whereas apart from these three patients with bradyarrythmias, no complications were noted following adenosine administration. On the basis of these observations, the authors of (14) reach, on page 79, the following conclusion: *"Intracoronary adenosine is a potent and very short-acting vasodilator. However its clinical applicability is limited by side effects and unpredictability of the dose needed to induce maximal hyperemic response in the coronary circulation."*

5.2 Therefore, although intracoronary adenosine was found in (14) to possess useful and advantageous properties as a pharmacological stressor for the assessment of coronary artery disease in human patients, such as a potent coronary vasodilating activity and an extremely short plasma half-life, the person skilled in the art would clearly see a serious limitation in its clinical usefulness and safety due to the above-cited side-effects and its unpredictability of the suitable dosage regimen.

5.3 Hence, citation (14) sets the skilled person the problem of providing means for improving the clinical usefulness and safety of adenosine or functional adenosine receptor agonists as a vasodilator for the diagnosis of coronary artery disease, myocardial

dysfunction, ischemic ventricular dysfunctions or in the assessment of the vasodilatory capacity of coronary arteries in conjunction with a non-invasive or invasive technique.

5.4 According to claim 1 this problem is solved by a modification of the dosage regimen used in (14), optionally in conjunction with a different mode of administration, that is to say, the solution of claim 1 comprises intravenous administration of adenosine or a functional adenosine receptor agonist as a new mode of administration in low doses of from 20 to 200 µg/kg/min, and intracoronary bolus injection, likewise in low doses of from 2 to 20 µg.

6. The question arises whether the problem defined above has indeed been solved in its different aspects by the features recited in claim 1.

6.1 The examples in the application illustrate the usefulness of adenosine as a pharmacological stressor for the detection of coronary artery disease as assessed

- by intravenous administration using the claimed dosage regimen in conjunction with thallium 201 scintigraphy (see Example I);

- by intravenous administration of adenosine using the claimed dosage regimen in conjunction with echocardiography (see Example II); or

- by intravenous or intracoronary administration of adenosine using the respective claimed dosage regimen in conjunction with measurements of coronary blood flow reserve using a Doppler flow catheter (see Example III).

In Example 1 (see especially page 12, lines 10 to 11; end of page 12; page 14, lines 1 to 4) mention is made that the adenosine infusion was either well tolerated in all subjects or, if side effects occurred, these were usually mild, did not require therapy and ceased instantly after discontinuing the adenosine infusion.

6.2 Accordingly, in view of the results obtained in the examples of the present application and in the absence of any evidence to the contrary, the board is satisfied that the problem as defined above is plausibly solved.

7. It remains to be examined whether, in view of the technical problem to be solved, the requirement of inventive step is met by the claimed use.

7.1 Adenosine has been shown in (14) to possess certain highly desirable advantages over conventionally used pharmacological stressors such as papaverine and dipyridamole. Apart from its strong coronary vasodilating effect, adenosine has an extremely favourable ultra-short plasma half-life of less than 20 seconds. According to the state of the art available in the proceedings, adenosine appears in this respect unequalled by other coronarodilatory agents hitherto used to assess coronary artery disease, such as papaverine and dipyridamole, as evidenced by the following data:

- time from the intracoronary bolus injection to the peak of hyperemic response: 7.4 ± 2.2 sec. for adenosine *vs*. 26 ± 0.3 sec. for papaverine;

- time from injection to subsidence of hyperemic response: 30 ± 5 sec. for adenosine *vs*. 108 ± 25 sec. for papaverine - see (14), pages 77 and 78;

- dipyridamole has likewise the disadvantage of a long-lasting duration of action which makes repeated assessment of different coronary vascular beds of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible - see (14), page 79, left-hand column, lines 1 to 8.

As a result of this favourable property of adenosine, the time required for testing is advantageously shortened and the diagnostic procedure accordingly causes less discomfort to patients.

7.2 Given these striking advantages associated with the application of adenosine as a pharmacological stressor, the skilled person had, in the board's judgment, a clear and strong incentive to investigate any promising route for improving the clinical usefulness and applicability of adenosine and solving the technical problem posed.

7.3 The skilled person seeking in the relevant state of the art a solution to the stated technical problem, would inevitably come across document (11) which he would have considered highly relevant for the following reasons:

Document (11) entitled *"Cardiovascular effects of adenosine in man; possible clinical applications"* provides a comprehensive view of the cardiovascular effects of adenosine when administered to human subjects. Chapter 7 is concerned with *"effects of exogenous adenosine"* and refers in the most relevant Section 7.2.1 to its use for coronary vasodilation. In the paragraph bridging pages 335 and 336 it is stated:

"In a second patient group, the effect of non-hypotensive infusion rates of adenosine was studied in subjects during bypass surgery. The blood flow was measured by electromagnetic flow probes on the coronary artery grafts during stable hemodynamic conditions before closure of the thorax. Adenosine (20 to 50 µg/kg/min) induces a 100% increase in the graft flow without affecting left ventricular work. There was a marginal effect on systemic blood pressure but no influence on the heart rate. The data demonstrate that intravenously administered adenosine can produce preferential coronary vasodilation in man. The postoperative ECG did not reveal signs of ischemia in any of these 10 cases. The possible clinical use of adenosine is discussed in Section 8.2."

In Section 8.2 , page 343, citation (11) goes on to state:

"Adenosine can be infused by the i.v. route at a low rate that induces clear-cut coronary vasodilation (see lines 1-2) <.....> However, the coronary vasodilators that have previously been tested are also associated with a fall in blood pressure and increase in heart rate. Since adenosine induces a marked and stable coronary vasodilation in these patients, without reducing the perfusion pressure or increasing the myocardial work, it may offer a new therapeutic approach in counteracting graft occlusion" (see lines 8 to 12).

Finally, Table 6 on page 345 of (11) refers to the use of adenosine in low doses of *20 to 50 µg/kg/min* to achieve *"Preferential myocardial vasodilation"* and recommends in this context the use of adenosine as a *"diagnosticum"*.

7.4 To summarise, the disclosure of document (11) provides the skilled person seeking a solution to the stated technical problem in the state of the art with the following teachings:

- intravenously administered adenosine produces preferential coronary vasodilation in man;

- adenosine infused by the i.v. route at a low rate induces clear-cut coronary vasodilation;

- intravenous administration of adenosine to a human subject in a dosage range of from 20 to 50 μg/kg/min [which falls within the range of from 20 to 200 μg/kg/min claimed in present claim 1] is capable of inducing a 100% increase in blood flow in a coronary artery graft flow without affecting left ventricular work;

- use of the dosage range suggested in (11) leads to predictable and reproducible effects in coronary vasodilation;

moreover, the administration and dosage regimen of adenosine used in (11);

- does not lead to undesired side effects, such as affection of left ventricular work or heart blockage;

- does not exhibit an effect on systemic blood pressure or, if at all, only a marginal effect;

- does not reduce the perfusion pressure or increase the myocardial work;

- does not influence the heart rate, i.e. does not induce bradyarrythmia.

7.5 Equipped with the knowledge and information mentioned above, the skilled person would, in the board's judgment, reasonably expect the technical problem posed to be successfully solved in all its aspects by the administration of adenosine to human subjects at the low dose range suggested in (11). In this respect it should be emphasised that he would find in (11) the explicit suggestion to use adenosine in the dosage range specified in the claims of the present application as a preferential myocardial vasodilator for diagnostic purposes (see especially page 345, Table 6).

Consequently, the side effects reported in document (14) and observed in three out of 12 patients cannot be regarded as a real prejudice, as alleged by the appellant, which would have prevented or diverted the skilled person from following the clear teaching in (11) and applying this teaching to solve the stated problem and overcome the difficulties and drawbacks reported in (14).

Moreover, the existence of a prejudice cannot normally be shown by one single piece of scientific literature (here document (14)), to the extent that it reflects the opinion, experience and knowledge of just one author but not the common general knowledge in the special field (see "Case Law of the Boards of Appeal of the EPO", 3rd edition 1998, I. D. 7.2). In the present case the skilled person with the knowledge of (11) would have readily realised that the side effects in three patients and the unpredictability of the required dosage reported in (14) were the result of using an unsuitably high dosage regimen in conjunction with intracoronary administration of adenosine.

7.6 During oral proceedings the appellant also drew attention to the results presented in Examples I and II which were intended to show the advantages implied by the use of adenosine over dipyridamol or papaverine. However, since neither of the two latter substances represents the closest prior art, these results are completely immaterial for assessing the existence of an inventive step. Furthermore, these advantages were already evident in the light of the disclosure in document (14).

7.7 In conclusion, the subject-matter of the main request and the first auxiliary request does not fulfil the requirement of inventive step and is therefore not patentable (Article 52(1) in conjunction with Article 56 EPC).

Second auxiliary request:

8. Compared with the main and the first auxiliary requests, claim 1 of the second auxiliary request (see paragraph VI above) relates to the sole use of adenosine in the preparation of a diagnostic agent,

(a) the adenosine acting as a pharmacological stressor,

(b) in conjunction with radioimaging of the coronary arteries,

(c) for patients who are unable to exercise adequately,

the regimen of administration being the same as that for the main and first auxiliary requests.

8.1 Document (14) represents the closest prior art. The problem underlying the invention claimed in the second auxiliary request as against document (14) comprises two independent aspects.

On the basis of the teaching in (14) that the unpredictability of the dose needed to induce maximal hyperemic response *makes adenosine an unsuitable agent for coronary vasodilation if a radiographic technique is used ..."* (see page 79, left-hand column, lines 11 to 17 from the bottom), the first aspect of the problem to be solved is that of providing means for improving the clinical usefulness and safety of adenosine as a pharmacological stressor for the diagnosis of coronary artery vascular disease in conjunction with radioimaging. It is evident that this aspect of the problem is already included in the one defined in relation to the main and first auxiliary requests, and represents a limited form thereof.

The second aspect of the problem to be solved is that of providing a new application of adenosine at the same conditions seen above.

8.2 The solution offered by claim 1 to the first aspect of the problem comprises adenosine in a unit dosage of 20 to 200 μg/kg/min for intravenous administration or in a dosage of 2 to 20 μg for intracoronary bolus administration.

The solution proposed to the second aspect of the problem is the administration to a human who is unable to exercise adequately.

As is evident the solution of the first aspect of the problem is substantially identical to the solution given in relation to the main and first auxiliary requests. On the basis of the considerations already

made under point 6 of the decision, the board is satisfied that this part of the problem is plausibly solved.

8.3 As to the inventive step involved in said proposed solution, the board wishes to make clear that feature (a), ie that adenosine acts as pharmacological stressor, merely expresses explicitly what was already implicit in the particular use of adenosine as a diagnostic agent according to the main and first auxiliary requests. Thus, it merely represents one of the possible definitions of the same pharmacological activity. Therefore, beyond any linguistic difference, the use of adenosine as a vasodilator and pharmacological stressor is the same in all three requests.

8.4 As to the feature (b), ie use of adenosine in conjunction with radioimaging of coronary arteries, the board finds that in the first paragraph on page 1 and in Example I of the application as filed it is recognised that the diagnostic techniques that were known in the state of the art and used to assess patients with known or suspected artery disease were non-invasive methodologies and in particular radioimaging such as radionuclide angiography or myocardial perfusion scintigraphy. Similarly, document (14) contains a reference to the use of papaverine in conjunction with radioimaging techniques (see end of the left-hand column on page 76). Moreover, there can be no doubt that non-invasive techniques such as radioimaging usually cause less discomfort to patients and therefore are preferred to invasive techniques.

For these reason, radioimaging in itself is not a framework which can endow the use of adenosine, as a pharmacological stressor, with an inventive step.

8.5 It should be emphasised that the main and first auxiliary requests already implied the use of adenosine in conjunction with invasive and non-invasive techniques in general. The use of adenosine in conjunction with radioimaging gives rise to the same type of drawback, ie clinical side-effects and unpredictability of the maximal hyperemia dosage (see document 14), as in conjunction with any other non-invasive technique, since these disadvantages are not caused by the technique used but by the very administration of adenosine.

Accordingly, the same considerations which led the board to conclude on the lack of inventive step of the main and first auxiliary requests in relation to any invasive or non-invasive techniques also apply in relation to a specific non-invasive technique (ie radioimaging) which suffers from the same problems.

8.6 The second aspect of the problem is allegedly solved by the use of adenosine as a pharmacological stressor in the preparation of a diagnostic agent to be given to "a human who is unable to exercise adequately".

The purpose of this feature would appear to be that of confining the use of the diagnostic agent to an allegedly novel sub-group of patients as compared to the patients referred to in the closest prior art, document (14).

8.7 In this context, the board makes reference to decisions T 19/86 (OJ EPO 1989, 25) and T 893/90 (22 July 1993, not published in OJ EPO). In the board's interpretation of both decisions, if the use of a compound was known in the treatment of a disease, the treatment of the same disease with the same compound could nevertheless represent a novel therapeutic or diagnostic application, provided that two conditions are met:

(i) the treatment must be carried out on a novel group of subjects which is clearly distinguishable with respect to its physiological or pathological status from and does not overlap with the group previously treated (see sero-positive *vs.* sero-negative piglets (T 19/86) or haemophilic patient vs. normal, non-haemophilic subjects (T 893/90);

(ii) the choice of the new group, if distinguishable from the known one, must not be arbitrary, which means that there must exist a functional relationship between the particular physiological or pathological status of this new group and the therapeutic effect obtained. In other words, the peculiar feature identifying the new group of patients must have a real impact on the result of the treatment, since it is able finally to "change" the treatment itself. In the case considered in T 19/86, protection caused by vaccination of seropositive piglets (ie already having protective antibodies) on the one hand and of seronegative piglets on the other was expected to be based on different physiological effects. Similarly, non-haemophilic subjects differ from haemophilic patients in their blood coagulation process, as this latter group lacks at least one essential blood-clotting factor. Thus, in case T 893/90, controlling bleeding in normal subjects, on the one hand, and curing the defective bleeding in haemophilic patients, on the other, was likewise based on different physiological effects.

8.8 The above considerations similarly apply to the use of a substance as a diagnostic agent. However, in the board's opinion, neither of the above cited conditions is met in the present case:

According to the description in the application as filed (see especially page 17, lines 11 to 13), adenosine has an advantage over exercise as a stressor in "*patients who are unable or unwilling to exercise at a work load appropriate for the non-invasive assessment of coronary artery disease*". Even if feature (c) is limited to patients who are unable to exercise adequately, this definition continues to be very vague and general. It embraces many, if not most of the situations in which a pharmacological stressor may be used, ranging from patients in an almost normal physiological condition, who might be only subjectively unable to exercise, to patients in a critical pathological condition, who are objectively incapable of exercise. Thus, feature (c) embraces at best a sub-group of those patients having coronary artery disease already being treated with adenosine according to document (14).

However, even in cases where the incapability of taking exercise was objective, as a result of an actual physical hindrance, there would still not exist, in the board's view, any functional relationship between the incapability of a patient to exercise adequately and the pharmacological effect achieved by the administration of adenosine in the diagnosis of various types of coronary disease. In fact, no evidence or argument was produced by the appellant to show any interaction between the physical hindrance and the hyperemic effect caused by adenosine.

Under these circumstances, it appears clear to the board that the reference to "a human who is unable to exercise adequately" cannot be regarded as a feature capable of distinguishing the subject-matter of claim 1 from the closest prior art. This feature cannot therefore contribute to the inventive step of the claimed subject-matter either.

9. In conclusion, the subject-matter of the second auxiliary request does not fulfil the requirement of inventive step either and is therefore not patentable (Article 52(1) in conjunction with Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

A. Townend C. Germinario