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D E C I S I O N
of 17 November 2005

Case Number: T 0445/01 - 3.3.02

Application Number: 91909913.5

Publication Number: 0527917

IPC: A61K 31/70

Language of the proceedings: EN

Title of invention:
Use of Adenosine and Adenosine derivatives for anesthesia

Patentee:
FUKUNAGA, Atsuo F.

Opponent:
ITEM DEVELOPMENT AB

Headword:
Adenosine for anesthesia/FUKUNAGA

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 69(1), 84, 100(a)(b), 106, 107, 108, 123(2)(3)
EPC R. 57(a), 64

Keyword:
"Admissibility of late-filed request (yes): request filed in response to objections raised for the first time in the pending proceedings"
"Allowability of the amended claims (yes): requirements of Articles 84 and 123(2) and (3) EPC met"
"Sufficiency of disclosure (yes): in the absence of any evidence to the contrary, the subject-matter now claimed can be considered to be adequately disclosed"
"Novelty (yes): new therapeutic application"
"Inventive step (yes): the new therapeutic application was not obviously derivable from any of the documents cited in the proceedings taken either in isolation or in combination with each other"

Decisions cited:
G 0005/83, G 0002/88, G 0006/88, T 0201/83, T 0219/83, T 0331/87, T 0728/98

Catchword:
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Case Number: T 0445/01 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 17 November 2005

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 26 February 2001 rejecting the opposition filed against European patent No. 0527917 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: J. Riolo
Members: G. Rampold
J. Seitz

Summary of Facts and Submissions

I. The respondent is proprietor of European patent No. 0 527 917 ("the patent") which was granted with effect from 21 January 1998 on the basis of European patent application No. 91 909 913.5 (International application No. PCT/US91/02951) filed on 7 May 1991, claiming priority from an earlier US application on 10 May 1990 (Serial No. 521 529).

II. The claims as granted read as follows:

"1. Use of adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate for the preparation of a composition for anesthetizing an individual of a mammalian species during noxious stimulation characterized in that said composition provides protection from pain or stress induced by the noxious stimulation, without causing cardio-respiratory depression.

2. Use according to claim 1 wherein said composition is administrable in a continuous infusion of between 1 µg/kg/min and 5000 µg/kg/min of said composition for the period that anesthesia is desired.

3. Use according to claims 1 or 2, wherein the composition is administrable via continuous intrathecal infusion.

4. Use according to claims 1 or 2, wherein the composition is administrable via continuous fractionated doses.

5. Use according to claims 1 or 2, wherein said pharmaceutical composition is administrable in a continuous intravascular infusion."

III. The appellant originally filed opposition to the grant of the patent requesting its revocation in full on grounds of lack of novelty and inventive step (Articles 100(a), 54 and 56 EPC) and also of insufficiency of disclosure (Articles 100(b) and 83 EPC).

IV. Of the numerous documents cited by the parties during the first-instance opposition or subsequent appeal proceedings, the following remain relevant to the present decision:

(1) A. F. Fukunaga et al, Anaesthesiology, vol. 71, No. 3A, September 1989, Abstract A260;

(2) P. A. Seitz et al, Anaesthesiology, vol. 71, No. 3A, September 1989, Abstract A264;

(3) M. Doi et al, Anaesthesiology, vol. 70, No. 2, February 1989, pages 360 to 363;

(4) S. Gröndal et al, World Journal of Surgery 12, 1988, pages 581 to 585;

(17) US-A-5 677 290

V. The opposition division of the European Patent Office, in a decision posted on 26 February 2001, rejected the opposition. The essence of the reasoning in the opposition division's decision was as follows:

(A) The disclosure of the claimed invention in the description of the patent in general and in Examples 1 to 3 in particular - although all these examples related to the use of adenosine in combination with a standard inhalational anesthetic - was sufficiently clear and complete for it to enable those skilled in the art to carry out the invention in its broadest embodiment without undue burden and to achieve the desired effects. In the opposition division's opinion, the use of adenosine, even if administered as the sole active agent for certain specific purposes stated in the claims, was adequately supported by the disclosure at lines 9 to 11 on page 4 of the patent where it was stated that "adenosine or adenine nucleotides may be the only agent required for certain uses, such as relief of chronic pain, and minor surgery where deep sleep is not necessary." In this respect the opposition division noted that the expression "for anesthetizing" in claim 1 is apparently to be construed as meaning "producing insensibility to pain".
It further noted that the opponent's allegation of insufficiency of disclosure was not supported by any evidence and concluded that the requirements of Article 83 EPC were fulfilled.

(B) The opposition division acknowledged both novelty and inventive step in respect of the claimed subject-matter. As regards novelty over the prior art of citations (1) and (2), it was held in the decision

under appeal that in both these citations the reported anesthetic effects of adenosine or ATP were accompanied with signs of severe hypotension. The opposition division considered that none of the citations available in the proceedings taught or suggested that significant decrease in blood pressure and cardio-respiratory depression, which were well documented adverse reactions taking the form of frequent and serious side-effects occurring after administration of adenosine or its phosphorylated derivatives (adenine nucleotides) in anesthesiology, could be avoided, and hemodynamic stability in patients was maintained, if the adenosine or adenine nucleotide was not administered as a surgical anesthetic to a patient in need of it until noxious stimulation during surgery had started.

(C) As regards novelty over the state of the art according to citations (3) and (4), the opposition division mentioned that in both citations adenosine was used for a different purpose from the claimed use, namely as an antihypertensive agent for the peroperative blood pressure control. It also mentioned that the skilled person could not derive from either (3) or (4) that administration of adenosine was useful to protect an individual during noxious stimulation from pain or stress induced by the noxious stimulation.

(D) As regards inventive step the opposition division concluded that, compared with the closest state of the art according to citations (1) and (2), the problem to be solved was to find a proper way of avoiding cardio-respiratory depression and undesirable hypotensive effects caused by the use of adenosine or its

phosphorylated derivatives as anesthetics. It concluded that this problem had been properly solved in the patent in an inventive manner by a specific mode of administration of adenosine or adenosine nucleotides as surgical anesthetics to a patient in need of it wherein the adenosine or adenine nucleotides were administered to the patient only when noxious stimulation during surgery had started. The opposition division thus found that the cited state of the art did not prejudice the maintenance of the patent as granted.

VI. On 17 April 2001, the appellant lodged an appeal against the adverse decision of the department of first instance, paid the corresponding fee and filed a statement of grounds of appeal.

VII. In a communication dated 24 June 2005 both parties were duly summoned to oral proceedings before the board, fixed for 7 September 2005. In a letter of 27 June 2005 the respondent's representative requested an adjournment of the oral proceedings *sine die*, on the grounds that, several months before the summons by the board she had already been summoned to oral proceedings in a different case before an examining division of the EPO on the very day appointed by the board of appeal for the hearing in the present case. Since the appellant agreed to an adjournment, the board summoned the parties to oral proceedings on the new date of 17 November 2005.

VIII. Both parties were represented at the oral proceedings. After detailed discussion of the question of novelty of the claimed subject-matter in the patent over the cited state of the art, the respondent requested a short

break for deliberation which was allowed. After the break the respondent filed an amended set of five claims forming its current main request and maintained the claims as granted as an auxiliary request.

The claims in the current main request differ from those as granted (see II above) in one aspect only; in present claim 1 the feature "during surgery" has been inserted between the terms "noxious stimulation" and "characterized in". Claim 1 as amended reads accordingly as follows, with the amendment highlighted in bold italic letters:

"Use of adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate for the preparation of a composition for anesthetizing an individual of a mammalian species during noxious stimulation ***during surgery*** characterized in that said composition provides protection from pain or stress induced by the noxious stimulation, without causing cardio-respiratory depression."

Dependent claims 2 to 5 remain identical to those as granted (see II above).

IX. The arguments of the appellant as submitted in writing and during the oral proceedings, in so far as they are relevant to the present decision, can be summarised as follows:

(1) As regards the ground for opposition mentioned in Article 100(b) EPC, namely that the patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person

skilled in the art, the appellant essentially relied on arguments in two directions:

(a) according to the appellant, the patent failed to sufficiently disclose the possibility of using adenosine or adenine nucleotides as the sole anesthetic agent for anesthetizing an individual of a mammalian species during noxious stimulation, without any initial or concomitant administration of a conventional anesthetic agent;

(b) the description (Example 2) demonstrated the absence of cardio-respiratory depression only at doses of ATP which were lower than those necessary to normally induce deliberate hypotension, as admitted by the respondent itself in Example 7 (see column 16, lines 16 to 17) of its own post-published patent specification (17). Thus, the patent did not, in the appellant's opinion, provide the skilled person with sufficient information whether and how cardio-respiratory depression could be avoided if adenosine or ATP was administered within the broad dosage range from 1 µg/kg/min to 5000 µg/kg/min specified in claim 2 of the patent at doses high enough to normally induce severe hypotension and cardio-respiratory depression in normotensive persons.

(2) As regards the opposition under Article 100(a) EPC on the ground of lack of novelty, the appellant essentially referred to the finding of the opposition division in the decision under appeal that in both citations (1) and (2) the anesthetic effects and inhibitory responses achieved by the administration of

adenosine or ATP were noted at the expense of severe hypertension. In this context, it was recalled by the appellant that in the decision under appeal (see Reasons, page 4, section II) the novelty of the claimed subject-matter in the patent had been acknowledged for the sole reason that, in contrast to the teaching of the patent, none of the citations in the proceedings taught that cardio-respiratory depression and severe hypertension, normally caused by the use of adenosine or its phosphorylated derivatives as surgical anesthetics, could be avoided if adenosine or its derivatives were administered to the patient only after the noxious stimulation during surgery had started.

(3) However, the appellant also indicated in its written submissions and orally at the hearing that citation (1) reported an experiment in animals which in all essential details was identical to the experiment described in Example 1 of the patent. According to the appellant, the respondent itself had admitted in its written submissions and at the hearing that Example 1 of the patent did **not** illustrate the invention since severe cardiovascular depression (hypertension) was caused by the use of adenosine in that example.

(4) The appellant went on to say that, in contrast to the respondent's submissions, the opposition division had expressed in the decision under appeal its opinion (see Reasons page 5, section IV.i) that the proprietor (respondent) had convincingly shown in **all Examples 1 to 3 of the patent** that the desired beneficial effects of the claimed invention could be achieved by carrying out the teaching of the patent. As regards Example 1 in the patent, the appellant thus saw some contradiction

between, on the one hand, the statements of the respondent, and on the other hand, the opinion of the opposition division in the decision under appeal. The appellant further noted that the opposition division had not answered its request for an explanation as to how the opposition division could arrive, in the contested decision, at the contradictory conclusion that **exactly the same experiment**,

- when reported in the prior art of (1), did not anticipate the claimed invention (see **(2)** above) but,

- when used in Example 1 of the patent to exemplify the claimed invention, demonstrated and verified the desired effects allegedly achieved by the claimed use of adenosine in the patent.

(5) On the basis of the following facts, namely

(i) the opposition division's finding that Example 1 in the patent demonstrated the claimed invention and

(ii) the identity of this example with the disclosure of citation (1),

the only reasonable conclusion that could be drawn, in the appellant's view, was that the claimed subject-matter lacked novelty over the prior art of (1).

(6) As regards the question of novelty of the claimed subject-matter in the patent over the prior art of citations (3) and (4), the appellant noted that in the

decision under appeal the opposition division was of the opinion (see especially Section II on page 4 of the Reasons) that in (3) and (4) adenosine or ATP was used for a different purpose, namely for counteracting the release of catecholamine in order to lower the increased blood pressure caused by the extensive release of catecholamines during pheochromocytoma removal. In this context, the appellant also referred in its submissions to the opposition division's further conclusion in the impugned decision, namely that the skilled person could not deduce from either (3) or (4) that pain and stress were influenced by the administration of adenosine because, in order to induce and maintain anesthesia during surgery, in both citations (3) and (4) various other anesthetics were used in amounts which *per se* were known to protect patients from pain and stress.

(7) It was recalled by the appellant that the opposition division and the respondent itself had admitted that in the surgical treatments reported in citations (3) and (4) anesthesia was induced in patients by thiopental and maintained with isoflurane and that adenosine was administered to the patients only after noxious stimulation had started. In particular, the appellant referred to the following teachings in the state of the art of (3) and (4) which, in its opinion, were relevant to the question of novelty in the present case:

(i) the clear teaching in both citations (3) and (4) to administer ATP or adenosine, respectively, to patients only after noxious stimulation had started;

(ii) the finding in the cited documents that this specific mode of administration did not cause the patients to become hypotensive although the doses as used were high enough to cause hypotension in a normotensive person not subjected to noxious stimulation (up to 0.6 mg/kg per min of ATP in (3): see page 360, right-hand column, lines 20 to 21; 50-500 µg/kg per min of adenosine in (4): see page 582, left-hand column, line 5 from the bottom).

(8) In the appellant's opinion the teaching of the cited state of the art referred to above must thus inevitably lead to the conclusion that the claimed subject-matter in the patent lacks novelty over the prior art of (3) and (4) contrary to the requirements of Article 54(1) EPC.
As regards the appellant's above conclusion of lack of novelty, it completed that conclusion with the following reasoning (see grounds of appeal, page 3, lines 25 to 30): *"It should be irrelevant in this connection whether (3) and (4) are recognizing the anesthetic effects of ATP or adenosine disclosed by (1) and (2) or not. (3) and (4) clearly teach a way to avoid hypotension caused by the administration of ATP and adenosine in patients subjected to noxious stimulation, namely to administer ATP and adenosine in such a rate that the patient does not turn hypotensive."*

(9) The appellant argued further that even if novelty were to be acknowledged, the claimed subject-matter would not involve an inventive step in the light of the

combined teachings of the cited documents. In particular, citations (1) and (2) suggested that clinical application of adenosine or adenine nucleotides as such might be beneficial in anesthesiology and pain management; the prior art of (3) and (4) taught a particular mode of administration of adenosine that did not cause the patients to become hypotensive even at dosage ranges high enough to cause hypotension in a normotensive person not subjected to noxious stimulation. The appellant concluded therefrom that the claimed subject-matter in the patent resulted from a simple combination of the cited state of the art, and therefore did not involve an inventive step.

X. The respondent disagreed, relying essentially on the following arguments:

(10) As to the appellant's objections on the grounds of insufficiency of disclosure, the respondent pointed to the disclosure on page 4, lines 9 to 11 of the patent where it is stated that "adenosine and adenine nucleotides may be the only agent required for certain uses, such as relief of chronic pain, or minor surgery where deep sleep is not necessary, but pain relief is. Major surgery may require the additional use of inhalational or intravenous anesthetics and some muscle relaxant." It concluded therefrom that the claims were not limited to the use of adenosine as the sole anesthetic agent and that the option of using adenosine as the sole active agent was sufficiently disclosed in the patent. It followed that the appellant's first objection under Article 83 EPC was unfounded.

(11) In the respondent's view, it was clearly taught in the contested patent that the dosage of adenosine to be administered to achieve the beneficial effects claimed in the patent depended on the intensity of the noxious stimuli and/or the desired depth of the anesthesia. In view of this correlation it was clear to those skilled in the art that administration of increased dosages of adenosine was necessary in cases of intense noxious stimulation. Apart from the fact that the dose of adenosine used was in any case limited by the wording of the claims to doses within the claimed range high enough to provide a satisfactory anesthetic effect without inducing cardio-vascular depression, the skilled person, on the basis of the information in the patent, was enabled to determine the required doses, without undue burden.

(12) With respect to the novelty issue, the respondent recalled that the principal author of citation (1) was the present inventor. This citation disclosed an animal experiment in which adenosine had been shown to reduce the anesthetic requirements for halothane. In this experiment the reduction of the MAC (minimum alveolar concentration) of the inhaled anesthetic halothane required to inhibit *50%* of movement in response to a tail clamp was determined. However, in these studies, the standard tail clamp stimulation was used and the inhibitory responses were noted at the expense of severe hypotension and cardiovascular depression.

(13) In contrast to the state of the art known from citations (1) and (2), the claimed invention in the patent resided in the finding that adenosine itself and also its mono-, di-, or triphosphate might be used as

surgical anesthetics in order to suppress pain or stress occurring during noxious stimulation during surgery, without simultaneously causing severe hypertension and cardio-respiratory depression. Claim 1 of the patent specifically related to the use of adenosine as the active ingredient of a composition for anesthetizing an individual of a mammalian species and for protecting said individual from pain or stress induced by noxious stimulation, without causing cardio-respiratory depression. In the appellant's opinion, the prior art of (1) or (2) did not teach or suggest such a composition.

(14) It was admitted by the respondent that the disclosure of citation (1) was identical with Example 1 of the patent as granted. However, the respondent argued that Example 1 was **not** included in the patent specification to illustrate the claimed invention but rather to clearly demonstrate the inadequacy of the "standard" prior art methods for testing anesthetic potency. The test method used in citation (1) and likewise in citation (2) called for an "all or none response" and its reliability was thus very limited. In this type of test it was not possible to accurately determine and quantify the level of painful stimulus caused to the test animal because the location of the clamp on the tail as well as the pressure applied by the person clamping the tail varied broadly. In the respondent's opinion, the test method reported in citation (1) and similarly in citation (2) could not be used to determine a clinically useful dose response relationship for the administration of adenosine according to the invention. According to the respondent, the experimental method of (1) was used in

Example 1 of the patent solely to demonstrate the distinction between the prior art method used in (1) and the new experimental method and technique developed by the present inventors and used in the other examples of the patent.

(15) Because the effects of adenosine and adenine nucleotides did not appear to modify tactile sensation a more discriminative and quantifiable stimulus was required to assess the antinociceptive activity of adenosine and adenine nucleotides properly. Electrical stimulation as shown in Example 2 of the patent, although not a selective stimulation, was useful for this purpose and mimicked surgical stimulation. Motor behaviour and touch stimulation remained unaffected by adenosine, although the animals were unresponsive to painful stimulation. The **hypnotic-anesthetic effect** of, and the **analgesic responses** to inhaled anesthetics (halothane, enflurane, isoflurane), intravenous opioids (morphine fenantyl), and intravenous adenosine and ATP were assessed using electrical tail stimulation with graded degree of electrical intensities. Thus, according to the respondent, for the first time the two distinct behavioural responses were recognisable depending on whether the predominant drug action was **sedative-hypnotic** or **analgesic.**

This required that a new experimental technique be developed by the inventor, which led to the surprising discovery that adenosine could be used as an anesthetic for preventing the patients from suffering pain and stress without simultaneously inducing cardio-respiratory depression. Only the use of the sensitive experimental protocol developed by the present

inventors made it possible to provide a quantifiable and reproducible noxious stimulation, and to find a close correlation between the dosages of adenosine to be administered and the intensities of noxious stimulation, i.e., pain, which could be correlated to the clinical setting.

(16) As regards the state of the art according to citations (3) and (4), the respondent noted as a preliminary issue that in the surgical treatments reported in both (3) and (4) only conventional anesthetic drugs were used for anesthetizing patients undergoing surgery. More specifically, in the surgical treatment (resection of pheochromocytoma) disclosed in citation (3), the patients were given diazepam, scopolamine and hydroxyzine as premedications. Anesthesia was then induced with thiopental and sevoflurane. During operation, anesthesia was maintained with 5% sevoflurane and 60% nitrous oxide (see (3), page 360, right-hand column, full paragraphs 2 and 3)).

Similarly, in the surgical treatment (pheochromocytoma removal) of citation (4), morphine was used for premedication; anesthesia was induced by thiopental and pancuronium and was maintained during surgery with high doses of isoflurane (1.5-2.5%) in 60% nitrous oxide in oxygen (see (4), page 581, lines 8 to 11 from the bottom).

(17) According to the respondent, severe hypertension and cardiac arrythmia were well documented known problems during surgical removal of pheochromocytoma (see (3) and (4)). This was due to the release of

extremely high levels of circulating catecholamines during tumor manipulation and removal. The respondent indicated that in both citations (3) and (4), adenosine and ATP were used as vasodilating drugs to treat severe hypertension and cardiac arrhythmias caused by the extensive release of catecholamine from the tumor (pheochromocytoma) during its surgical manipulation and removal. Thus, in the cited documents adenosine and ATP were advantageously used as vasodilators in order to replace other previously used conventional vasodilating drugs, such as, for example, sodium nitroprusside (SNP) or phentolamine and to effectively and promptly control hypertension (see especially (4), the paragraph bridging the left-hand and right-hand column of page 581).

(18) The respondent thus concluded that adenosine and ATP were administered in (3) and (4) for an entirely different therapeutic application and for treating entirely different medical conditions. Adenosine and ATP were not administered in the cited document for the purpose of inhibiting pain and stress during surgery. The fact that adenosine exhibited strong analgesic and/or anesthetic effects was neither recognized nor in any way suggested by the authors of (3) and (4).

(19) The respondent noted that according to the case law of the boards of appeal an inherent, but as yet undisclosed effect, is no bar to novelty.
Even if one assumed that in (3) and (4) the administration of adenosine might have inherently resulted in an analgesic and/or anesthetic effect, this was not recognized in the cited documents and was thus "not made available to the public" within the meaning

of Article 52(4) EPC. In accordance with the principles set out in G 2/88 (OJ EPO 1990, 93) and G 6/88 (OJ EPO 1990, 114), such an undisclosed effect, even if it was inherent in the known use of adenosine or ATP disclosed in (3) and (4), conferred novelty on the claimed use in the patent over the cited state of the art.

(20) The problem to be solved by the claimed invention was, in the respondent's opinion, to find a method of anesthesia which is safer for patients than conventionally used methods. In this respect the respondent was confronted with the task of minimising the hypotensive and/or cardio-respiratory depressant effects of conventional agents used in anesthesia. In the respondent's view, no teaching permitting these disadvantages to be obviated was shown in the embodiments described in the state of the art available in the proceedings. In particular, the prior art contained no teaching or suggestion and thus provided no clue to the solution of the problem addressed in the patent.

(21) In particular, the prior art, in the respondent's opinion, contained no teaching or suggestion that the cardio-respiratory depressive effects of adenosine could be avoided while achieving the desired anesthetic effect. In view of the fact that the state of the art available in the proceedings indicated that adenosine could cause, for example, severe hypotension, bradycardia, and even pain, the skilled person would have been diverted away from the claimed use of adenosine and adenine nucleotides in the patent.

XI. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the decision under appeal be dismissed and that the patent be maintained either on the basis of the main request filed during the oral proceedings, or as granted (auxiliary request).

Reasons for the Decision

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

2. *Admissibility of the late-filed request (current main request)*

2.1 As is apparent from paragraph VIII above, the current main request was only presented by the respondent at a very late stage of the proceedings, namely during the hearing before the board. Its admissibility into the proceedings is thus a matter for the board's discretion. It is well-established by the jurisprudence of the boards of appeal that, in considering the admissibility of late-filed requests into the proceedings, account is to be taken, *inter alia*, of whether they could have been filed earlier and if so the reason why they were not, and of their relevance and in particular whether such requests were filed in reaction to any new submissions, objections or arguments brought up by a party or the board for the first time during the pending proceedings (see generally, "Case Law of the Boards of Appeal of the European Patent Office", 4th edition, 2001, pages 324 to 333). In addition to these

general principles, the board must also ensure that late filing does not take another party by surprise and that, if a late request is to be admitted, the other party or parties have sufficient time to consider it and, as appropriate, reply with a new request of their own.

2.2 In the circumstances of the present case, the board considers that the current main request should be admitted into the proceedings, in spite of its late filing.

2.3 The respondent's assertion that this request formed a response to the objections raised by the appellant and the reservations expressed by the board during the hearing concerning the novelty of claim 1 as granted over the prior art of citations (1) and (2) appears *prima facie* correct. That said, the current main request was submitted by the respondent more than four years after the statement of the grounds of appeal was filed and the board does not condone such lateness *per se*. However, in the circumstances of this case it was immediately clear to the skilled reader that the only difference between claim 1 as granted and claim 1 as per the newly filed main request was the insertion of the feature "during surgery" between the words "during noxious stimulation" and "characterizing" (see VIII above) and neither the appellant nor the board had any difficulty to understand the meaning and scope of the proposed amendment. Coupled with the facts that novelty of the claims as granted over the prior art of (1) and (2) was acknowledged in the proceedings before the department of first instance and that the appellant to a large extent prompted this amendment by its own

arguments, the board exercises its discretion in favour of the respondent.

2.4 In view of the above, the amendment to claim 1 can fairly be said to be occasioned by a ground for opposition specified in Article 100(a) EPC and to constitute a *bona fide* attempt on the part of the respondent to overcome certain of the appellant's objections to lack of novelty and inventive step of the claimed subject-matter over citation (1), raised in the opposition and appeal statements and, in particular, at the hearing before the board. The proposed amendment to the granted patent is thus admissible also under the terms of Rule 57a EPC.

3. *Allowability of the amendment; Article 123(2) and (3) EPC*

3.1 In accordance with the established jurisprudence of the EPO boards of appeal, the decision on the compliance of amendments with Article 123(2) EPC calls for an inquiry into whether or not the application as originally filed contains sufficient information so that the person skilled in the art could derive the proposed amendments from it directly and unambiguously, including any features implicit therein (see e.g. T 201/83, OJ EPO, 1984, 481; T 331/87, OJ EPO, 1991, 022; T 728/98, OJ EPO, 2001, 319; and in general "Case Law of the Boards of Appeal of the EPO", 4th ed. 2001, pages 197 ff).

3.2 Pursuant to Article 123(2) EPC the original disclosure, i.e. in the present case the content of international application No. PCT/US91/02951, published under the PCT

as WO 91/16903, determines the scope of possible amendments.

3.3 The amendment which was incorporated in present claim 1 ("during surgery") is not such that the patent contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC). Furthermore, the claim as amended is supported by the description (Article 84 EPC). In particular, the feature "during surgery" can be directly and unambiguously derived , *inter alia*, from

(a) the first paragraph on page 9 (*"As used herein "anesthesia" is defined as the final result of several interacting but independent effects. The first effect is sedation and/or sleep induction; the second is analgesia or pain relief; the third is stress reduction to preserve physiological homeostasis, most frequently seen as blood pressure modification* ***during surgery;*** *and finally, the fourth is usually considered to be muscle relaxation, particularly relaxation of skeletal muscle. At the present time, no single agent provides adequate levels of each and all of these four effects, so combinations of drugs must be used in cases like surgery. Anesthetic as used herein will refer to any single drug that gives rise to at least two of the four effects");*

(b) the paragraph bridging pages 9 and 10 (*"As used herein* ***"surgery"*** *and* ***"surgical procedures"*** *refer broadly to invasive discomfort—producing medical procedures. Included are such procedures as endoscopy, angiography, dental work, such as tooth*

extractions, as well as what is traditionally thought of a ***surgery****, for example appendectomies and the like <.....>");*

(c) the second full paragraph on page 10 *("As used herein "stress" refers to the physiological changes that accompany trauma such as* ***surgery");*** and

(d) the end of the first paragraph on page 13 (*"In particular, no currently used anesthetic agent has much effectiveness against the stress induced by* ***surgery"****);*

(e) furthermore, in addition to the specific disclosures mentioned above, the added feature "during surgery" in the context of the other features of claim 1 is **clearly implied by and therefore derived from the whole disclosure** as such of the application as originally filed.

3.4 The insertion of the additional feature "during surgery" narrows the scope of protection conferred in comparison with claim 1 as granted so that the requirements of Article 123(3) EPC are also met.

4. *Sufficiency of disclosure; Article 100(b) EPC*

4.1 An attack on the ground of insufficiency under Article 100(b) EPC is, of course, based on Article 83 EPC which requires that the disclosure of the invention must be "sufficiently clear and complete for it to be carried out by a person skilled in the art". It is understood that this means that substantially any

embodiment of the invention, as defined in the broadest claim, must be capable of being realised on the basis of the disclosure.

4.2 As a preliminary point in connection with the appellant's objections under Article 100(b) EPC, in the present case the board considers it useful and appropriate to focus attention on what is in fact claimed in the broadest claim 1 of the contested patent.

Claim 1 is directed to the "use of adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate for the preparation of a composition **for anesthetizing** an individual of a mammalian species **during noxious stimulation during surgery** characterized in that said composition provides protection from pain or stress induced by the noxious stimulation, without causing cardio-respiratory depression."

Page 4 of the patent, lines 9 to 11, states: "Adenosine or adenine nucleotides may be the only agent required for certain use, such as relief of chronic pain, or minor surgery where deep sleep is not necessary, but pain relief is. Major surgery may require the additional use of some inhalational or intravenous anesthetics and some muscle relaxant."

4.3 From the foregoing it is clear that claim 1, interpreted in conjunction with the description pursuant to Article 69(1) EPC, defines the use of adenosine or adenosine nucleotides

(i) either as the sole agent

(ii) or in combination with some additional inhalational or intravenous anesthetic for **anesthetizing** an individual of a mammalian species **solely and exclusively during the period** of noxious stimulation during surgery, in order to protect said individual from pain or stress induced by the noxious stimulation, without causing cardio-respiratory depression.

4.4 With respect to its first objection of insufficiency under Article 100(b) EPC the appellant essentially argued that the patent failed to sufficiently disclose the option (i) of using adenosine or adenine nucleotides as the sole anesthetic without the **initial** or **concomitant** administration of any other conventional anesthetic agent. This argumentation first of all fails to take into account the fact that the **optional use** of adenosine or adenosine nucleotides **as the sole anesthetic agent** for anesthetizing an individual envisaged in the patent and claimed in present claim 1 is *per definitionem* strictly **limited to the period of noxious stimulation during surgery** (see 4.3 above) and does thus of course **not** exclude the preceding administration of any conventional inhalational or intravenous anaesthetic, for example, to induce anesthesia.

4.5 Apart from the fact that the appellant has failed to provide any evidence in support of its mere allegation that the option of using adenosine or adenosine nucleotides as the sole anesthetic agent during the period of noxious stimulation during surgery [in particular in cases "of minor surgery where deep sleep is not necessary, but pain relief is"] would be

clinically impossible, this particular option is clearly and sufficiently disclosed in Example 2 of the patent. Thus, page 5, lines 36 to 41, states: "ENF (enflurane) concentrations of 0.5, 1.0, 1.5, 2.0, 2.5% were added to N_20 stepwise; responses and blood gases were recorded; in addition to electrical stimulation, the tail, ear and leg were clamped with a hemostat, and pinprick was applied to reconfirm responses to nociception. When negative response to stimuli was achieved, the dose of ENF was decreased stepwise by 0.5% till positive response was shown; then, ATP infusion was titrated to replace the decreased ENF anesthesia till **ATP could totally and effectively replace ENF** (ATP initial dose: 5 µg/kg/min)."

4.6 With respect to its further objection of insufficiency under Article 100(b) EPC the appellant essentially argued that the patent did not provide the skilled person with sufficient information as to how cardio-respiratory depression can be avoided when adenosine or adenosine nucleotides are administered within the broad dosage range from 1 µg/kg/min to 5000 µg/kg/min specified in claim 2.

By arguing merely that because claim 2 covers a broad dosage range, whereas Example 2 of the Patent specifically discloses that addition of increasing doses of ATP of 5-70 µg/kg/min allowed ENF to be replaced without diminishing the pain tolerance and without causing cardio-respiratory depression (see page 5, lines 44 to 46), the appellant has not adequately substantiated the claim of invalidity, in the absence of any evidence that there exists at least one dose falling within the range given in claim 2

which would cause cardio-respiratory depression **following the exact teaching of the patent**. Here the appellant has the burden of proof, and has failed to discharge it (see T 219/83, OJ EPO 1986, 211).

4.7 From Example 2 and Figures 3 and 4 of the patent is indeed derivable that the intensity of noxious stimulation correlates with the dose of adenosine administered. Example 2 expressly mentions that, in the tests carried out, electrical stimulation in increasing voltage, as tolerated, up to 50v was applied and that this allowed quantifiable and reproducible stimulation (see especially page 5, lines 34 to 36). Thus, the dosage of the administered adenosine or ATP can be higher if the intensity of the noxious stimuli is higher and *vice versa*. In the board's opinion the gist of the invention underlying the patent was the finding that the administration of doses of adenosine which are high enough to normally induce deliberate hypertension and cardio-respiratory depression in a healthy individual do not exhibit these undesirable side-effects if administered to the same individual during noxious stimulation.

4.8 This is strongly supported by *post-published* document (17) which was cited by both parties and is therefore introduced in the present decision. For example, as illustrated in Figure 4 of document (17), the blood pressure was recorded as electrical stimulation was applied to the tail. When ATP was administered, purposive escape movements decreased. When **sufficient ATP, i.e. 1000 µg/kg/min,** was infused, **no** further purposive escape movements or **stress were seen as reflected by the blood pressure** (see Figure 4 and

column 12, lines 55 to 60), in other words no signs of hypertension or cardio-respiratory depression were observed during noxious stimulation at a dosage of ATP of 1000 µg/kg/min which, if administered to a subject not suffering pain, would normally induce severe hypertension. In this respect it is noted that from (17) is also derivable that doses of ATP that would not induce deliberate hypertension in a normotensive person are as low as, for example, 108±21 µg/kg/min (see column 12, lines 16 to 17).

4.9 In view of the foregoing observations and in the absence of any evidence showing the contrary, the board has no doubt that the disclosure is enabling and that the requirements of Article 100(b) EPC are met.

5. *Novelty; Articles 52(1) and 54 EPC*

5.1 As appears from paragraph VIII above, claim 1 is drafted in the conventional "second (further) medical use" format ("Swiss type claim"). The claim contains the following features (lettering of the features added by the board):

(a) Use of adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate
(b) for the preparation of a composition
(c) for anesthetizing an individual of a mammalian species
(d) during noxious stimulation
(e) during surgery

characterized in that

(f) said composition provides protection from pain or stress induced by the noxious stimulation,

(g) without causing cardio-respiratory depression.

5.2 In accordance with the principles set out in decision G 5/83 (OJ EPO 1985, 64) and the substantial body of case law which has been developed by the boards of appeal in this respect (see eg "Case Law of the Boards of Appeal of the European Patent Office", 4th edition, 2001, I. C. 5.2, pages 88 to 94), the concept of "second (further) medical use" can only be applied to claims to the use of known substances or compositions (here adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate) for the preparation of a medicament intended for use in a method referred to in Article 52(4) EPC. This is clearly the case here.

5.3 The Enlarged Board derived the novelty of such claims from their sole new feature, that is the new pharmaceutical use of that known substance.

5.4 In the present case, the appellant in its written submissions and at the oral proceedings challenged the novelty of claim 1 on the basis of citations (1), (2), (3) and (4). A claimed invention lacks novelty unless it includes at least one essential technical feature which distinguishes it from the cited state of the art. When deciding upon the novelty of a claim, a basic initial consideration is therefore to construe the claim in order to determine its technical features (see 5.1 above).

5.5 Both **citations (1) and (2)** disclose studies of the effects of intravenously administered adenosine and ATP on the halothane MAC in animal models. The MAC was determined in both citations using the standard tail clamp technique (clamping the proximal one-third of the shaved tail with a rubbershod hemostat closed to first ratchet (see (1), left-hand column, lines 5 to 8 from the bottom; see (2), left-hand column, second paragraph, lines 1 to 2).

5.6 The teaching in claim 1 as amended to use adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate for anesthetizing an individual of a mammalian species during noxious stimulation **during surgery** [see ***feature (e)***] cannot be regarded as disclosed explicitly or by implication either in citation (1) or citation (2) and therefore, in the context of the other features of claim 1, defines a **novel therapeutic application** in accordance with the principles set out in the above-mentioned decision of the Enlarged Board. This confers novelty on the claimed subject-matter in the patent over the state of the art according to citations (1) and (2).

5.7 In view of the foregoing it is also clear that Example 1 of the patent no longer falls within the scope of claim 1 as amended. Thus, the question whether or not Example 1 illustrates the claimed invention becomes irrelevant.

Citation (3) refers to the anesthetic management in five patients during resection of pheochromocytoma.

5.7.1 According to the disclosure of (3), **anesthesia** was induced with 150—200 mg of thiopental iv and 4—5% of sevoflurane. Intubation of the trachea was facilitated with 20 mg of alcuronium iv. The induction of **anesthesia** was smoothly performed in four of five cases. In patient 4 circulation was severely changed during the induction of anesthesia. After infusion of 200 mg of thiopental arterial blood pressure increased to 200/124 mm Hg and heart rate increased to above 100 beats/min. Arterial blood pressure and heart rate could not be controlled with 5% sevoflurane and 60% nitrous oxide inhalation. **Then ATP was infused up to 0.6 mg/kg^{-1}/min^{-1}. Arterial blood pressure then decreased rapidly**, but heart rate remained above 100 beats/min. Therefore 0.4 mg of propranolol iv successfully decreased heart rate. Orotracheal intubation was then performed without any complication. During operation **anesthesia** was maintained with inspired concentrations of 1.6—4.9% sevoflurane, 35—50% oxygen and 50—65% nitrogen for patients 1 2 and 3 and with inspired concentrations of 1-5% sevoflurane, 50—65% nitrous oxide and 35—50% oxygen for patients 4 and 5. Inspired and end tidal sevoflurane concentrations were monitored with a mass spectrometer in patients 1, 2 and 3. In patients 4 and 5 inspired sevoflurane concentration was estimated from the dial of the precalibrated vaporizer (see page 361, right-hand column, full paragraphs 2 and 3).

5.7.2 As regards the pharmacological use and therapeutic application of ATP, citation (3) imparts the following teaching:

During tumor manipulation 0.1—1.2 $mg/kg^{-1}/min^{-1}$ of **ATP was used as a vasodilator** in all patients. Although surgical maneuver made plasma catecholamnine concentrations significantly high, **hypertension** was controlled promptly, and tachycardias were prevented with increasing inhaled sevoflurane concentrations and ATP infusion rates in patients 1, 3 and 5. In patients 2 and 4, because plasma norepinephrine concentrations were extremely high, heart rate could not be controlled completely with sevoflurane and ATP, so propranolol 0.4 mg (patient 2) and 3.2 mg (patient 4) was given iv (see (3): especially bridging pages 360 and 361).

5.8 **Citation (4)** discloses, *inter alia*, that "during surgical removal of pheochromocytoma, large amounts of catecholamines (CA) are released from the tumour into circulation during manipulation, causing a potentially dangerous increase of blood pressure of the systemic and pulmonary circulation" and that "pharmacological control of blood pressure peroperatively is, thus, mandatory and usually accomplished by SNP or phentolamine" (see page 581, the paragraph bridging left-hand and right-hand columns).

5.8.1 Furthermore citation (4) clearly states that "**anesthesia** was induced by thiopental (4-5 mg/kg) and pancuronium (0.1 mg /kg) was given to facilitate tracheal intubation. **Anesthesia** was maintained with isoflurane (1.5-2.5% in 60% N_2O in oxygen). Before and during induction of anesthesia, and during and after operation, samples of arterial blood were drawn for determination of fractionated plasma CA" (see page 581, right-hand column, lines 5 to 11 from the bottom).

5.8.2 As regards the pharmacological use and therapeutic application of adenosine, citation (4) imparts the following teaching:

"At induction of anesthesia or during surgical manipulation of the tumor, or both, all patients presented a rapid increase of arterial BP, heart rate and cardiac output. **Adenosine** infusion was started with a low dose (50-100 µg/kg per min) and rapidly adjusted by dose steps of 50 µg/kg per min **in order to prevent the BP from exceeding 200 mm Hg**. An infusion rate of 50-500 µg/kg per min limited BP to a range of 120—200 mm Hg in all patients. **The BP normalizing effect of adenosine was rapid** and the appropriate infusion rate was obtained within 90 sec from the start of infusion. Adjustments of the **adenosine** dose gave a prompt effect and a stable BP of 120—150 mm Hg was easily managed. The CA-induced increase in mean pulmonary artery pressure was also effectively reduced, although this **adenosine** response was slower at onset and required 5—10 minutes to achieve the full effect. None of the patients had any cardiac arrhythmias throughout the operation and no beta-blocking agents were, therefore, required" (see (4), page 582, the paragraph bridging the left-hand and right-hand columns).

"Severe, life-threatening hypertension, cardiac arrhythmias, and problems in obtaining pharmacological control of these parameters during removal of pheochromocytoma are well known. The pretreatment of patients with long-acting alpha- and beta-receptor blocking drugs has reduced the reactivity of the circulation, but continuous surveillance and

pharmacologic intervention is mandatory during the operation. In spite of the advent of phentolamine, SNP, nitroglycerine, and propranolol, peróperative episodes of **severe hypertension** and arrhythmias occur in more than *50%* of the patients. This is due to the extremely high plasma CA levels and their rapid and large changes during pheochromocytoma surgery. The endogenous nucleoside **adenosine** has a pharmacologic profile making it suitable for peroperative use. It has a half-life of less than 10 seconds and exerts its main vasodilatory effect by decreasing systemic vascular resistance. Furthermore, **adenosine** probably causes a powerful postjunctional antagonistic interaction with CA in different vascular beds and **adenosine** inhibits the myocardial responses to CA [7]. **Adenosine** in high doses has an inhibitory influence on sinus node automaticity and atrioventricular conduction . Thus, the actions of **adenosine** seem to be ideal in the treatment of **CA-induced hypertension and possibly also for arrhythmias.** In the present 10 patients, BP was rapidly controlled by **adenosine** although the plasma CA levels were extremely high in some patients. These results, therefore, illustrate that **adenosine** can be used also as a peroperative antihypertensive drug, at a dose range similar to that used for peroperative controlled hypotension. The lack of cardiac ventricular arrhythmias suggests that **adenosine** also counteracts the arrhythmogenic effect of elevated CA levels" (see (4), page 583, the paragraph bridging the left-hand and right-hand columns).

5.9 To summarise: both citations (3) and (4) disclose the **peroperative** use of adenosine [i.e. the use of adenosine during noxious stimulation during surgery

[see **features *(d) und (e)*** in 5.1 above] **as a vasodilator** for the treatment and control of CA-induced hypertension and arrhythmias (see 5.7.2 and 5.8.2 above).

5.9.1 However, the teaching in present claim 1 to use adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate (ATP)

- **for anesthetizing** an individual of a mammalian species [see ***feature (c)*** in 5.1 above]

- during noxious stimulation during surgery [see features (d) und (e) in 5.1 above]

- in order to provide protection from pain or stress induced by noxious stimulation [see feature (f) in 5.1 above]

- without causing cardio-respiratory depression [see feature (g) in 5.1 above]

cannot be regarded as disclosed either in citation (3) or citation (4). Feature (c) in the context of other features of claim 1 therefore defines a **therapeutic application** for adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate (ATP) which is disclosed neither in citation (3) nor in citation (4). There is no disclosure in these citations suggesting to the skilled reader that adenosine or ATP as such exhibits a potent anesthetic action which could be used to replace at least partially or even totally any of the conventional anesthetics used in (3) or (4). This confers novelty on the claimed subject-matter in

the patent over the state of the art according to citations (3) and (4).

5.10 In its statement setting out the ground of appeal and during the oral proceedings before the board, the appellant essentially argued that both citations (3) and (4) clearly disclose the administration of adenosine or ATP to patients during noxious stimulation during surgery. It also argued that according to both citations such administration did not introduce hypotension in the patients treated, even if adenosine or ATP was administered within a dosage range which normally causes severe hypotension in normotensive persons not subjected to noxious stimulation.

The appellant concluded therefrom that the claimed use in the patent lacked novelty over the state of the art of citations (3) and (4). In the appellant's opinion it was in the present case irrelevant to the issue of novelty whether or not the anesthetic effects of adenosine or ATP had already been recognized in the state of the art according to (3) and (4) (see e.g. statement of grounds of appeal, page 3, second full paragraph). The board cannot share the appellant's opinion.

5.11 In the above-mentioned submissions, the appellant appears to be of the opinion that in a case like the present one where a compound has previously been described as having been used, but for a different purpose from the claimed use, and **the previously described use had inherently had the same technical effect as the claimed use**, there was a lack of novelty (so-called "doctrine of inherency"). The board would

emphasise that under Article 54(2) EPC the question to be decided is what has been "made available" to the public; the question is not what may have been "inherent" in what was made available (by a prior written description, or in what had previously been used, for example). Thus, the question of "inherency" does not arise as such under Article 54 EPC. This point may be illustrated by a further reference to the facts of the present case. If the claims are interpreted as discussed in paragraphs 5.9 and 5.9.1 above, the question in relation to novelty is whether documents (3) and (4) made available to the public the technical teaching that adenosine or ATP, when used as described, exhibits potent anesthetic properties. Thus, although citations (3) and (4) describe the treatment of patients with adenosine or ATP in order to regulate their blood pressure and to control hypertension and arrhythmias, such treatment, when carried out, would inevitably have been inherently a use of such compounds for anesthetizing an individual of a mammalian species during noxious stimulation during surgery. Nevertheless the anesthetic effects of adenosine and ATP underlying the claimed use was not "made available" to the public within the meaning of Article 54(2) EPC by the prior written description in citation (3) or (4).

5.12 On the basis of the above considerations, the board has come to the conclusion that the claimed subject-matter in the main request is novel with respect to the prior art of citations (1) to (4).

6. *Inventive step; Articles 52(1) and 56 EPC*

6.1 In the view of the board, the closest state of the art is represented by Fukunaga et al (1), describing the effects of intravenously administered adenosine and ATP on the halothane MAC in rabbits. Both ATP and adenosine alone were shown in (1) to exhibit potent anesthetic properties which could partly or even totally replace the halothane MAC. In these animal studies, the standard tail clamp stimulation was used, and the inhibitory responses were noted at the expense of severe hypotension (see (1), especially left-hand column: Methods, end of the first paragraph and right-hand column: Discussion).

6.2 In the light of the disclosure in (1) as representing the closest state of the art, the problem to be solved by the claimed invention can be seen to consist in finding for adenosine, adenosine monophosphate, adenosine diphosphate, or adenosine triphosphate further or additional properties or effects forming the basis for a new and valuable application of these compounds, for example in the field of medicine.

According to present claim 1, this problem is solved by the proposed use of adenosine or its phosphorylated derivatives for anesthetizing an individual of a mammalian species during noxious stimulation during surgery in order to protect said individual from pain or stress induced by the noxious stimulation during surgery, without causing cardio-respiratory depression.

On the basis of the disclosure of the claimed invention in the patent, and in the absence of any evidence to

the contrary, the board is satisfied that the problem stated above has been credibly solved.

6.3 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.

6.3.1 The person skilled in the art faced with the stated problem and seeking a solution in the closest state of the art according to (1) would have learned that administration of exogenous adenosine or ATP may reduce the anesthetic requirement during inhaled anesthesia. The person skilled in the art would, however, also have learned that concomitant administration of a strong adrenergic medicament (phenylephrine) was necessary to support blood pressure and to avoid severe hypotension and inadequate cardiac and respiratory activity caused by the administration of adenosine. Similarly, citation (2) discloses that adenosine in doses which produce arterial hypertension significantly reduces halothane requirements in dogs and suggests that these properties of adenosine should have substantial value in anesthesia during controlled arterial hypotension.

From the observations above it is clear that the severe side-effects associated with the use of adenosine or ATP as anesthetics have been recognised in citations (1) and (2), but both citations would teach away from the claimed solution and point those skilled in the art in the direction of administering an additional medicament to support blood pressure and to avoid cardio-respiratory depression.

6.3.2 Regarding the prior art of (3) and (4), it should first be noted that the subjects treated in (3) and (4) are suffering from pheochromocytoma and form a **specific class of patients** that are at risk of extreme, often fatal, hypertension due to an adrenal gland tumor that causes excessive release of catecholamines, particularly during manipulation of the tumor. Thus the board does not recognise any contradiction to the fact that under the **very specific conditions** of the surgical treatment disclosed in (3) and (4) adenosine and ATP exhibit a strong vasodilating and hypotensive effect, while under the conditions of the claimed invention adenosine or ATP can be used for anesthetizing an individual of a mammalian species during noxious stimulation during surgery, without any significant decrease in blood pressure.

In any case, neither of citations (3) and (4) suggests that adenosine in anesthetized subjects may have antinociceptive properties or that adenosine or adenine nucleotides, when not administered until noxious stimulation during surgery has started, can render analgesia effective without cardio-respiratory decompensation, including significant decrease in blood pressure and cardio-respiratory depression. There was no indication or hint whatsoever in the cited documents that clinical application of adenosine may be beneficial in anesthesiology and pain and stress management.

6.3.3 Finally, the fact that the claimed invention afforded the development of a new experimental technique and test method by the inventor in order to make the two distinctly different effects of adenosine or adenine

nucleotides during anesthesia recognisable, depending on whether the predominant drug action was sedative-hypnotic or analgesic, can be regarded as a further indication of inventive step.

6.4 The board is thus satisfied that the requirements of Article 52(1) in conjunction with Article 56 EPC are also met.

7. The conclusions above extend not only to the subject-matter of claim 1 but also to that of claims 2 to 5; these claims are dependent on claim 1 and relate to specific embodiments of the use according to claim 1 (see II above).

8. Since the main request is allowable, there is no need to examine the auxiliary 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 maintain the patent on the basis of the following documents:

- Claims 1 to 5 as filed during the oral proceedings
- Description pages 2 to 6 as granted
- Figures 1 to 4 as granted

The Registrar: The Chairman:

A. Townend J. Riolo