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Datasheet for the decision of 12 August 2010

Case Number: T 0294/07 - 3.3.04

Application Number: 00940519.2

Publication Number: 1187635

IPC: A61K 45/06

Language of the proceedings: EN

Title of invention:
Anaesthetic formulation comprising an NMDA-antagonist and an alpha-2 adrenergic agonist

Patentee:
Protexeon Limited

Opponent:
L'AIR LIQUIDE, S.A.

Headword:
Anaesthetic formulation/PROTEXEON

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request - inventive step (yes)"

Decisions cited:
G 0002/08, T 0939/92, T 1319/04, T 1329/04

Catchword:
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Case Number: T 0294/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 12 August 2010

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 22 December 2006 revoking European patent No. 1187635 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: R. Gramaglia
Members: M. Wieser
D. S. Rogers

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietor (Appellant) against the decision of the Opposition Division, whereby the European patent No. 1 187 635 was revoked pursuant to Article 102(1) EPC 1973.

II. The patent, which had been granted with a set of twelve claims, had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Articles 100(b) EPC.

The Opposition Division decided that the patent according to Appellant's main request, claims 1 to 12 as granted, met the requirements of Articles 54 and 83 EPC, but that the claimed subject-matter did not involve an inventive step, contrary to the requirements of Article 56 EPC. Also the subject-matter of the claims according to Appellant's first, second and third auxiliary requests was found not to meet the requirements of Article 56 EPC.

III. The Board expressed its preliminary opinion in a communication dated 7 November 2008.

In a further communication dated 8 April 2009 the Board drew the parties' attention to decision T 1319/04 of 22 April 2008 which referred three questions to the Enlarged Board of Appeal (EBA). As the answer to these questions was considered to be perhaps relevant for the present case, the Board suggested staying the procedure until the EBA had answered these questions.

In agreement with the parties the proceedings in the present case before the Board of Appeal were stayed until proceedings before the EBA, pending as G 2/08, in respect of the questions referred to in decision T 1319/04 (supra) were terminated.

In a communication dated 12 March 2010 the parties were informed that decision G 2/08 had been published. They were summoned for oral proceedings.

The Respondent informed the Board that it would not be present at the oral proceedings.

Oral proceedings were held on 12 August 2010 in the absence of the Respondent.

IV. The Appellant requested that the decision under appeal be set aside and as a main request, that the patent be maintained as granted, or alternatively, that the patent be maintained on the basis of one of auxiliary requests 1 to 5, all filed with letter of 23 April 2007.

The Respondent requested in writing that the appeal be dismissed.

V. Claim 1 as granted read:

"1. An anaesthetic formulation comprising xenon and an alpha-2 adrenergic agonist."

Dependent claims 2 to 5 referred to preferred embodiments of the formulation according to claim 1.

Claims 6 to 8 read as follows:

"6. Use of xenon in the manufacture of a pharmaceutical composition for the induction and/or maintenance of anaesthesia, wherein the xenon is for use in combination with an alpha-2 adrenergic agonist.

7. Use of an alpha-2 adrenergic agonist in the manufacture of a pharmaceutical composition for the induction and/or maintenance of anaesthesia, wherein the alpha-2 adrenergic agonist is for use in combination with xenon.

8. Use of xenon and an alpha-2 adrenergic agonist in the manufacture of a pharmaceutical composition for the induction and/or maintenance of anaesthesia."

Dependent claims 9 to 12 referred to preferred embodiments of the use according to claims 6 to 8. According to claim 10 xenon and the alpha-2 adrenergic agonist were "administered consecutively, sequentially, simultaneously or a combination thereof."

VI. The Appellant's arguments can be summarised as follows:

The closest prior art was represented by document (3). The problem underlying the patent was the provision of improved xenon containing anaesthetic formulations, more specifically, of formulations with improved neuroprotective activity.

This problem has been solved as shown by the experimental data of Annex 2.

The surprising and unexpected synergistic neuroprotective effect was a class effect of all alpha-2 adrenergic agonists.

The combination of xenon and alpha-2 adrenergic antagonists was not obvious upon a combination of documents (3) and (2) and the synergistic effect could not therefore be considered as being merely a bonus effect.

VII. The Respondent's arguments in writing can be summarised as follows.

When considering the disclosure in document (3) the problem underlying the patent in suit was simply to find an adjunctive anaesthetic agent to combine with xenon. To select an alpha-2 adrenergic agonist was obvious in the light of the disclosure in document (2).

The patent did not contain any evidence to substantiate the existence of a synergistic neuroprotective effect of the claimed formulations. Alpha-2 adrenergic agonists were known as anaesthetic agents and their choice was purely arbitrarily and did not result in any unexpected effect.

Even if such an unexpected synergistic effect would have been shown by the patent, which definitely was not the case, it had to be considered that the examples exclusively referred to the administration by injection of a liquid formulation containing xenon and dexmedetomidine.

VIII. The decision refers to the following documents:

(2) Anesthesiology, vol.75, no.2, 1991, pages 252 to 256

(3) EP-B-0 864 329

(4) CNS Drug Reviews, vol.11, no.3, pages 273 to 288

(Annex 2) submitted by the Appellant with letter dated 28 September 2006

Reasons for the Decision

1. The Opposition Division decided that the subject-matter of claims 1 to 12 as granted was novel and sufficiently disclosed.

In the appeal procedure the Respondent has not put forward any objection under Articles 54 and 83 EPC. The Board has no such objections either.

2. For the assessment of inventive step (Article 56 EPC) the Board applies the problem-and-solution approach, which, as a first step, requires the definition of the closest state of the art.

3. The Board agrees with the Opposition Division and both parties that document (3) represents the closest state of the art, which is concerned, as is the present patent, with the provision of a xenon containing anaesthetic formulation.

In claim 15 and in paragraphs [0037] and [0038], document (3) discloses that the xenon containing preparation may additionally contain an intravenous anaesthetic, analgesic, seditative or muscle relaxant.

4. The problem to be solved by the patent in suit was the provision of an improved anaesthetic formulation (page 2, lines 13 to 14 of the original application published as WO 00/76 545; corresponding to paragraph [0006] of the patent.

The claimed formulation is distinguished from the preparations according to document (3) by containing an alpha-2 adrenergic agonist.

5. In order to decide whether the requirements of Article 56 EPC are met, it has to be examined if the problem as formulated above has indeed been solved by the subject-matter claimed, and if the claimed solution is not obvious in the light of the disclosure in the prior art.

6. N-Methyl-D-Aspartate (NMDA) antagonists, like xenon, are known to be neuroprotective under many clinically relevant circumstances (page 3, lines 27 to 28 of the application as published; paragraph [0014] of the patent). Also alpha-2 adrenergic agonists are known to be neuroprotective, for instance during ischemic insults (page 7, lines 6 to 8 of the application as published; paragraph [0026] of the patent).

According to page 11, lines 18 to 19 of the application as published (paragraph [0044] of the patent), the

neuroprotective action of the claimed formulation "is more efficacious as a result of the complementary action of the two components".

7. The patent does not contain experimental data proving the existence of a synergistic neuroprotective effect of the claimed anaesthetic formulations containing xenon and an alpha-2 adrenergic agonist.

However, during the opposition procedure, with letter dated 28 September 2006, the Appellant has submitted Annex 2, disclosing the results of *in vitro* and *in vivo experiments* investigating the neuroprotective activity of combined xenon an dexmedetomidine dosage. The *in vivo* data are derived from seven-day old postnatal rat pups which underwent right common carotid artery ligation. One hour after recovery from surgical procedure, they were exposed to a hypoxic environment and concurrent administration with either air (control), 6.25 µg/kg subcutaneous dexmedetomidine, xenon or a combination of both. The data show that xenon or dexmedetomidine alone had no significant neuroprotective effect. In contrast, where a combination of both agents was used, there was a marked reduction in infarction size, indicative of a significant neuroprotective effect. Statistical analysis confirmed that the effect was synergistic (see Annex 2, pages 1 and 5 to 9).

8. The Board is aware of decision T 1329/04 of 28 June 2005, wherein the competent Board stated that the definition of an invention as being a contribution to the art, i.e. solving a technical problem and not merely putting forward one, requires that it is at

least plausible by the disclosure in the original application that its teaching indeed solves the problem it purports to solve. Therefore, although supplementary post-published evidence may in the **proper circumstances** also be taken into consideration, it may not be considered at all if it is the first disclosure going beyond mere speculation.

The invention in the present case is concerned with an anaesthetic formulation comprising two compounds which per se are known in the art to be used as anaesthetics and which are described as having some neuroprotective activity in certain clinical situations. The application as published contains a statement that the neuroprotective activity of a formulation containing both agents is higher than it could be expected to be (see point (6) above) and comprises six examples wherein the claimed formulations were administered to human patients.

In the light of the principles underlying decision T 1329/04 (supra) the Board considers this to be a case where from the disclosure of the original application it is plausible that the problem underlying the invention, namely to provide an improved anaesthetic formulation, has indeed been solved. Thus, in addition post published evidence (Annex 2) may also be taken into consideration. This evidence discloses a synergistic neuroprotective effect of the claimed formulation.

9. Annex 2 exclusively refers to a formulation comprising xenon and dexmedetomidine, the latter being one member of the group of alpha-2 adrenergic agonists. Thus,

results in the form of experimental data which show that the technical problem underlying the present application has indeed been solved, have only been provided for one member of a group of compounds.

10. According to established case law of the Boards of Appeal, the extent of the monopoly conferred by a patent should correspond to and be justified by the technical contribution to the art. This general principle of law also applies to decisions under Article 56 EPC 1973, because everything covered by a legally valid claim has to be inventive (see Case Law of the Boards of Appeal, 5th Edition 2006, Chapter I.D.1).

11. Decision T 939/92 (OJ EPO 1996, 309) contains fundamental rulings on broad claims in the field of chemistry. The Board in case T 939/92 held that in view of the state of the art the technical problem which the patent in suit addressed was provision of further chemical compounds with herbicidal activity. It was necessary for all the claimed compounds to possess this activity. The question as to whether or not such a technical effect was achieved by all the chemical compounds covered by such a claim might properly arise under Article 56 EPC, if this technical effect turned out to be the sole reason for the alleged inventiveness of these compounds. The Appellants' (Patent Proprietors') submission that the test results contained in the description showed that **some** of the claimed compounds were indeed herbicidically active could not be regarded as sufficient evidence to lead to the inference that substantially **all** the claimed compounds possessed this activity. In such a case the

burden of proof rested with the Appellants. The requirements of Article 56 EPC had not therefore been met.

Claim 1 of the main request of the application underlying decision T 939/92 referred to a triazole sulphonamide defined by its formula, which contained three residues designated (R1), (R2) and (R3). A list of possible substituents for each of these three residues was indicated in the claim, which also included three provisos. Thus, the claim, although not referring to an indefinite number of compounds, encompassed a large group of compounds whose exact size could not be judged at first sight. Moreover, as stated in detail in point 2.6.2 of decision T 939/92, the Appellants' own submissions with regard to several prior art documents on file were such that a person skilled in the art would have been unable to predict, on the basis of his general knowledge, that all claimed compounds would have herbicidal activity.

12. Contrary to this, the Appellant in the present case has put forward detailed arguments why the synergistic effect detected in the examples described in Annex II was not restricted to dexmedetomidine, but was a class effect shared by all members of the group of alpha-2 adrenergic agonists.

In detail it was highlighted that alpha-2 adrenergic agonists constituted a class of drugs, which, independent of their chemical structure, were defined by their specific target, namely the alpha-2 receptors. Dexmedetomidine, an example of this group, demonstrated a 1600-fold selectivity for alpha-2 over alpha-1

receptors. The actions of dexmedetomidine could therefore be attributed solely to its effects on the alpha-2 receptor.

It has been shown that the action of dexmedetomidine can be blocked by atipamezole, a highly selective alpha-2 antagonist (see document (4), abstract and page 277, first full paragraph). Accordingly, because dexmedetomidine and atipamezole were so selective for alpha-2 receptors, it could be stated with confidence that synergy would also occur with other alpha-2 agonists.

Further support for this argument could be found by considering the mechanicsm of the synergy on neuronal level, and in particular at the synaptic junction. Xenon had been shown to block the action of glutamate on NMDA receptors and to hyperpolarize the post synaptic membrane. Likewise the alpha-2 agonist dexmedetomidine acted on alpha-2 receptors, either pre- or post-synaptically, to cause hyperpolarisation. However, when xenon and dexmedetomidine were administered in combination, the hyperpolarisation synergistically enhanced the efficacy of xenon as an NMDA antagonist. As the synergy could be explained functionally, there was every reason to believe it would hold true for other alpha-2 agonists, irrespective of their structure.

13. In the light of these arguments, which have not been called into question or even commented on by the Respondent, the Board is convinced that the present case can be distinguished from T 939/92 (supra).

14. The Respondent additionally argued that the examples of the patent all referred to the administration by injection of a liquid composition comprising xenon and dexmedetomidine. Any unexpected effect, even if it existed, was not shown for any other route and/or mode of administration.

The Respondent has not provided any evidence to substantiate this argument. Any conclusion that the synergistic effect shown by the examples of Annex 2 can only be achieved when using a specific route and/or mode of administration is therefore considered as being an unproven allegation.

Without any evidence to the contrary on file the Board arrives at the decision that the problem underlying the patent in suit, namely the provision of improved anaesthetic formulations, has been solved over the entire scope of the claimed subject-matter.

15. The Opposition Division decided in the decision under appeal that a skilled person, trying to solve said problem, would have combined the teaching in document (3) (see point (3) above) with the teaching in document (2) and would have arrived at the claimed subject-matter in an obvious way. It found that the synergistic effect evidenced by the Patent Proprietor (Appellant) was "merely a bonus effect of the obvious combination".

16. According to the established case law of the Boards of Appeal, an effect which was to be expected as the result of an obvious measure could not contribute to recognition of the required inventive step, even if the scale of this effect was surprising to the skilled

person. In such a case an effect whose scale surpassed the skilled person's hopes merely represented a bonus effect following inevitably from the use of an obvious measure and obtained by the skilled person without an inventive effort on his part (see Case Law of the Boards of Appeal of the EPO, 5th Edition, 2006; Chapter I.D.9.7).

It has to be examined therefore, whether the combination of xenon and alpha-2 adrenergic agonist was an obvious measure for the skilled person, that is, as repeatedly formulated by the Boards of Appeal, whether the skilled person was in a "one-way-street" situation, when being confronted with the problem underlying the patent in suit.

17. Document (3) itself discloses in paragraphs [0037] and [0038] on pages 5 and 6, a list of roughly fifty substances that could be added to xenon as a further anaesthetic, analgesic, seditative of muscle relaxant. This list does not contain alpha-2 adrenergic agonists. Moreover, document (3) does not mention that the addition of any of the listed substances has any influence on the neuroprotective activity of xenon.

Document (2) demonstrates that dexmedetomidine, an alpha-2 agonist, produces a hypnotic-anaesthetic response in rats and concludes, that, if the animal data can be extrapolated to the clinical paradigm, it "may be more useful as an adjunctive anaesthetic agent." (see abstract and page 255, last paragraph). The document does not refer to the neuroprotective activity of dexmedetomidine or to its influence on the neuroprotective activity of another anaesthetic agent.

18. The patent, disclosing in paragraph [0026] that alpha-2 agonists such as dexmedetomidine, are known in the art to have neuroprotective activity, refers also to various considerations a skilled person would have before applying alpha-2 agonists in a clinical setting. It is stated in paragraph [0026] that "the use of alpha-2 adrenoceptor agonists in general anaesthetic practice has been hampered by their lack of anaesthetic potency and side-effect profile." The lack of potency required the use of very high doses which could result in peripheral vasoconstriction with an increase in blood pressure. Furthermore, alpha-2 agonists have been found to be preconvulsant in some models of epilepsy. Finally, in paragraph [0029] it is said that biologically important adaptations to the immediate effects of alpha-2 agonists, a phenomenon generally termed "tolerance", may lead to a diminished drug effect over time. While tolerance to certain actions are considered to be desirable, "it may mitigate the clinical utility of alpha-2 agonists for chronic pain relief and prolonged sedation in the intensive care setting."

19. Accordingly, the Board sees no "one-way-street" situation for a skilled person, who, starting from the disclosure in document (3), tries to provide improved anaesthetic formulations. Rather on the contrary, being aware of the undesired side-effect profile of alpha-2 adrenergic agonists, the skilled person would have a tendency not to add it to a xenon containing anaesthetic formulation.

The Board decides therefore that the claimed subject-matter is not obvious in the light of the disclosure in document (3) when combined with the teaching in document (2) or any other document on file. The determined synergistic neuroprotective effect of the claimed formulation is not therefore a bonus effect following inevitably from an obvious measure.

20. Claims 6 and 7 refer to the use of one of the two active agents of the formulation of claim 1 for the manufacture of a pharmaceutical composition for the induction and/or maintenance of anaesthesia, which is for use in combination with the other active agent, respectively. Claim 8 relates to the use of both active agents for the manufacture of a pharmaceutical composition.

The Board decided above that an anaesthetic formulation comprising xenon and an alpha-2 adrenergic agonist is novel and inventive within the meaning of Articles 54 and 56 EPC.

The same applies to the use of an anaesthetic composition containing either the one or the other of the two active agents in combination with the other active agent, respectively.

Decision G 2/08 of 19 February 2010 is concerned with a situation where it is already known to use a medicament to treat an illness and answers the questions whether or not this medicament can be patented for use in a different treatment of the same illness, even in cases when this treatment differs from the state of the art by a different dosage regimen only.

Therefore, decision G 2/08 does not apply in the present case.

21. The subject-matter of claims 1 to 12 as granted involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided:

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 as granted.

Registrar: Chairman:

P. Cremona R. Gramaglia