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**Datasheet for the decision
of 6 June 2011**

Case Number: T 1685/10 - 3.3.02

Application Number: 04021889.3

Publication Number: 1498124

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:

The use of inhibitors of the renin-angiotensin system

Patentees:

Ark Therapeutics Limited, et al

Opponents:

LES LABORATOIRES SERVIER
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
Merck & Co., Inc.
Sanofi-Aventis Deutschland GmbH

Headword:

RAS-inhibitors/ARK THERAPEUTICS LTD., ET AL

Relevant legal provisions:

EPC Art. 83

Relevant legal provisions (EPC 1973):

-

Keyword:

"All requests: sufficiency of disclosure (no): insufficient tests"

Decisions cited:

T 0433/05

Catchword:

-



Case Number: T 1685/10 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 6 June 2011

Appellants:
(Patent Proprietors)

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted 18 June 2010
revoking European patent No. 1498124 pursuant
to Article 101(2) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
R. Cramer

Summary of Facts and Submissions

- I. European patent No. 1 498 124 based on application No. 04 021 889.3, which is a divisional application of application No. 98 947 698.1, was granted on the basis of 14 claims.

The sole independent claim reads as follows:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment or prevention of stroke or its recurrence in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and wherein said inhibitor is selected from quinapril, captopril, perindopril, trandolapril, enalapril, moexipril, fosinopril, ramipril, cilazapril, imidapril, spirapril, temocapril, benazepril, alacepril, delapril, moveltipril, losartan, valsartan, irbesartan, candesartan, eprosartan, tasosartan and telmisartan."

- II. Four oppositions were filed against the patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC for amendments that contained subject-matter extending beyond the content of the parent application as filed.

- III. The documents cited during the opposition and appeal proceedings included the following:

(41) F.H. Messerli, et al., Arch. intern. med. (2003)
2557-2561

- IV. The appeal lies from a decision of the opposition division pronounced on 4 May 2010 revoking the European patent.
- V. In said decision the opposition division decided that the subject-matter of claim 1 as granted did not meet the requirements of Article 76 EPC, as the deletion of several compounds from the list of active agents and the selection of stroke from the list of diseases resulted in compositions that had no basis in WO 99/20260 (hereafter "the original application"). The same applied to dependent claim 6. Claim 1 of auxiliary request 1 was found to be allowable under Articles 76 and 123(2) EPC. However, the opposition division came to the conclusion that the invention as defined in auxiliary request 1 lacked sufficiency of disclosure as far as the treatment of stroke was concerned. In this context, it was emphasised that the only specific example did not work, so that further information for carrying out the invention was required which, however, neither the contested patent nor the available prior art nor the general knowledge of the skilled person provided. For the same reason, the invention as defined in auxiliary requests 2 to 4 also lacked sufficiency.
- VI. The patentees (appellants) lodged an appeal against that decision.
- VII. In the statement of the grounds of appeal the appellants requested accelerated appeal proceedings.

VIII. With a letter dated 6 May 2011, the appellants filed auxiliary requests 1 to 8. The sole independent claims of each request read as follows:

(i) Auxiliary request 1:

Claim 1 is identical to claim 1 as granted, except that captopril and enalapril were deleted from the list of active agents.

(ii) Auxiliary request 2:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment or prevention of stroke or its recurrence in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and wherein said inhibitor is selected from ramipril, losartan, valsartan, irbesartan, candesartan, eprosartan, tasosartan and telmisartan."

(iii) Auxiliary request 3:

Claim 1 is identical to claim 1 of auxiliary request 2, except that ramipril was deleted from the list of active agents.

(iv) Auxiliary request 4:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment or prevention of stroke or its recurrence in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and

wherein said inhibitor is selected from ramipril, losartan, valsartan and irbesartan."

(v) Auxiliary request 5:

Claim 1 is identical to claim 1 of auxiliary request 4, except that ramipril was deleted from the list of active agents.

(vi) Auxiliary request 6:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment or prevention of stroke or its recurrence in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and wherein said inhibitor is losartan.

(vii) Auxiliary request 7:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the prevention of stroke or its recurrence in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and wherein said inhibitor is selected from quinapril, perindopril, trandolapril, moexipril, fosinopril, ramipril, cilazapril, imidapril, spirapril, temocapril, benazepril, alacepril, delapril, moveltipril, losartan, valsartan, irbesartan, candesartan, eprosartan, tasosartan and telmisartan."

(viii) Auxiliary request 8:

"1. The use of an inhibitor of the renin-angiotensin system for the manufacture of a medicament for the treatment of stroke in a human patient, wherein the stroke is thrombotic or hemorrhagic, cerebrovascular or accident in origin, and wherein said inhibitor is selected from quinapril, perindopril,trandolapril, moexipril, fosinopril, ramipril, cilazapril, imidapril, spirapril, temocapril, benazepril, alacepril, delapril, moveltipril, losartan, valsartan, irbesartan, candesartan, eprosartan, tasosartan and telmisartan."

IX. Oral proceedings were held before the board on 6 June 2011.

X. The appellants' arguments in connection with sufficiency of disclosure can be summarised as follows:

For sufficiency, it was enough that there was some plausible indication in the original application that the invention would work. This was the case, as the original application mentioned mountaineering experiments which showed that certain populations could use oxygen more efficiently than others. This ability could be explained as a mitochondrial effect. Further data showed that said effect was linked to a particular polymorph of the ACE gene (ACE = angiotensin converting enzyme) and that these populations were characterised by a reduced RAS activity (RAS = renin-angiotensin system) which could be mimicked in other populations by administration of RAS-inhibitors in order to offer relative protection to tissues from periods of reduced oxygen supply, which includes the treatment or

prevention of stroke. Although the active agent used in example 1 (lisinopril) of the contested patent turned out to be ineffective for the treatment or prevention of stroke, example 1 was nevertheless important as it demonstrated the principle underlying the claimed invention: it showed that RAS-inhibitors increased the potential difference across the inner mitochondrial membrane and thus optimised ATP synthesis. The skilled person knew that lisinopril was too hydrophilic for crossing the blood-brain barrier and would therefore select a more lipophilic RAS-inhibitor. In this context, it was again emphasised that for sufficiency, it was not necessary to show that each compound included in the claims solved the technical problem. Neither was it necessary to use nerve cells instead of the heart muscle cells according to example 1, as the principle mentioned above was based on a more efficient functioning of the mitochondria, which were the same in both cell types. The appellants contested the argument of respondent 1 that treatment of stroke required active agents which were capable of promoting reperfusion by reasoning that the blood supply to the brain did not rely on a single artery, so that other blood vessels took over if the main supply route was impeded. In addition, the brain cells were not directly connected to the blood vessels but linked to them indirectly via the interstitial fluid, so that it was important to get a sufficient amount of active agent into said interstitial fluid.

"Prevention of stroke" meant any method that was suitable for preventing the consequences of a stroke. It did not include the prevention or treatment of any possible cause of stroke.

XI. The respondents' arguments in connection with sufficiency of disclosure can be summarised as follows:

Regarding the treatment or prevention of stroke, the contested patent only contained unsubstantiated assertions which could not establish sufficiency of disclosure. Example 1, which was the only example remaining in the contested patent, was defective for several reasons: it only concerned an *in vitro* test in which rat cardiomyocytes instead of human nerve cells were used. Moreover, the active agent used in this test increased the potential difference across the inner mitochondrial membrane but was nevertheless ineffective in the treatment or prevention of stroke.

As regards the meaning of "prevention of stroke", the respondents held that the definition proposed by the appellants was too narrow, as prevention of stroke included prevention of the cause of stroke.

XII. The appellants requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims as granted (main request) or, alternatively, on the basis of one of the auxiliary requests 1 to 8 filed with the letter of 6 May 2011.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.
2. Admissibility of auxiliary requests 1 to 8

These requests were filed at a late stage of the appeal proceedings, i.e. one month before the oral proceedings before the board. The admissibility of these requests is therefore at the board's discretion and depends upon the overall circumstances of the case under consideration (see Article 13 RPBA).

- 2.1 Regarding auxiliary requests 1 and 6 to 8, the amendments were made to overcome objections concerning insufficiency and to further delimit the subject-matter of the claims from the prior art. They were of a simple nature and did not take the respondents by surprise.
- 2.2 As regards auxiliary requests 2 to 5, it is noted that these requests correspond to auxiliary request 1 to 4 of the decision under appeal.
- 2.3 As a consequence, the board decided to admit auxiliary requests 1 to 8 into the proceedings (Article 13 RPBA). This was not contested by the respondents.
3. Sufficiency of disclosure - main request
- 3.1 The invention as defined in claim 1 of the main request relates to the use of specific RAS-inhibitors for the manufacture of a medicament for the treatment or prevention of stroke or its recurrence in a human patient. Where a therapeutic application is claimed in

the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, in order to meet the requirements of sufficiency of disclosure, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application, i.e. the suitability for the treatment or prevention of stroke or its recurrence (see T 0433/05 of 14 June 2007, point 28 of the reasons for the decision).

- 3.2 The contested patent as well as the original application disclose the theory that renin-angiotension systems (RAS) are implicated in the regulation of cellular metabolic efficiency, which can be enhanced by down-regulating the activity of RAS, resulting in a reduction of angiotensin II activity and an increase of kinin activity. Said enhanced metabolic efficiency, which can be explained as a mitochondrial effect, can be used for the protection of tissues from periods of reduced oxygen supply (see page 5, lines 9-21 of the original application). This theory is based on human data from mountaineering and trainability experiments which reveal that populations having an ACE-gene with a specific allele are able to use oxygen more efficiently than others (see page 20, line 9 to page 22, line 21 of the original application). Individuals with such an ACE-gene have reduced RAS activity. It was concluded that this effect could be mimicked by RAS-inhibitors in order to limit cerebral tissue damage in connection with stroke (see page 6, lines 27-31 of the original application).

3.3 Neither the contested patent nor the original application contains any direct evidence demonstrating the suitability of RAS-inhibitors for treatment or prevention of stroke or its recurrence. The sole example of the contested patent (corresponding to example 1 of the original application) shows that the RAS-inhibitor lisinopril increases the mitochondrial membrane potential of rat cardiomyocytes. There is no direct link to the treatment or prevention of stroke in this test, but it was concluded therefrom that RAS-inhibitors may protect against ischaemic situations and/or improve mechanical/biosynthetic performance by increasing the efficiency of energy transduction in the mitochondrion (see paragraph [0038] of the contested patent and page 24, lines 5-8 of the original application).

3.4 However, at least to the extent that the ischaemic situations mentioned above include stroke, this conclusion was later disproven by post-published clinical trials, which show that lisinopril and captopril increase the rate of stroke (see page 2558, last sentence of the central column to line 10 of the right-hand column and table 1 of document (41); see also point 7.4 of appellants' letter dated 19 November 2008). In other words: document (41) shows that the conclusions drawn in paragraph [0038] of the contested patent and page 24, lines 5-8 of the original application, which were based on the *in-vitro* test involving lisinopril, were unfounded so that there was lack of sufficiency at the effective filing date of the contested patent.

3.5 The appellants held that the *in-vitro* test of example 1 was meaningful despite the disclosure of document (41), as it demonstrated the principle behind the claimed application. Lisinopril was not suitable for the treatment of stroke because of its high hydrophilicity, which prevented its crossing the blood-brain barrier. However, these facts were known to the skilled person, who would conclude from the *in-vitro* test of the contested patent and from the disclosure of document (41) that other less hydrophilic RAS-inhibitors could be used for the treatment of stroke.

3.6 This argumentation cannot succeed. The board acknowledges that, according to the established jurisprudence of the boards of appeal, *in-vitro* tests may constitute a suitable tool for demonstrating a therapeutic effect of a compound or composition. However, the conditions of the test must be carefully selected and should correspond as closely as possible to the *in-vivo* conditions. If, as was alleged by the appellants, the skilled person knew about the problems of lisinopril in connection with crossing the blood-brain barrier, it would have been necessary and appropriate to select a less hydrophilic RAS-inhibitor for the *in-vitro* test. Moreover, the *in-vitro* test according to example 1 of the contested patent is further deficient in that caridomyocetes (heart muscle cells) rather than the cells affected by a stroke, i.e. nerve cells isolated from the brain, were used. The board cannot accept the appellants' argument that the cell type is irrelevant in view of the fact that the test was directed to mitochondria, which are ubiquitous.

- 3.7 Notwithstanding the fact that mitochondria are identical in all living cells of the body, there are nevertheless anatomical differences between nerve cells and muscle cells which may influence factors such as concentration of the active agent within the cell or its accessibility to the mitochondria.
- 3.8 To summarise: both the contested patent and the original application disclose the fact that individuals with reduced RAS activity can use oxygen more efficiently. This fact was backed up by the *in-vitro* test of the contested patent. Neither the test nor the general description contains a direct link to the treatment or prevention of stroke or its recurrence. The *in-vitro* test was not conducted *lege artis*, as it differs in two important aspects from the *in-vivo* conditions: (a) the selection of the active agent, and (b) the selection of the cell type. The *in-vitro* test is therefore meaningless. Moreover, the conclusion that RAS-inhibitors might be suitable for the treatment or prevention of stroke or its recurrence, which had been drawn on the basis of said *in-vitro* test, was subsequently disproven by *in-vivo* tests. The skilled person, relying on a careful selection of the test conditions and knowing that such tests are usually carried out by selecting particularly preferred active agents, has no reason to assume that these contradictory results are caused by an unsuitable active agent. He would rather deduce that the conclusions drawn from the theory mentioned above (see first sentence of point 3.2 above) and the results obtained by the *in-vitro* test in connection with stroke were not correct. As a consequence, neither the contested patent nor the original application discloses

the suitability of the product to be manufactured for the treatment or prevention of stroke or its recurrence (see last sentence of point 3.1 above) so that there is insufficiency of disclosure (Article 100(b) EPC).

4. Sufficiency of disclosure - auxiliary requests 1 to 6

The invention defined in claims 1 of auxiliary requests 1 to 6 differs from the invention according to claim 1 of the main request in that the list of active agents has been shortened. Deletion of active agents from the claims has no influence on the above argumentation concerning insufficiency, even if the list of active agents is reduced to a single compound as is the case in auxiliary request 6. As a consequence, the reasoning set out in point 3 above applies *mutatis mutandis* to the invention defined in auxiliary requests 1 to 6. The requirements of Article 83 EPC are therefore not met.

5. Sufficiency of disclosure - auxiliary request 7

The invention defined in claim 1 of auxiliary request 7 differs from the invention according to claim 1 of the main request by restricting the application of the medicament to the prevention of stroke or its recurrence and by shortening the list of active agents. These amendments have no influence on the above argumentation concerning insufficiency. As a consequence, the reasoning set out in point 3 above applies *mutatis mutandis* to the invention defined in auxiliary request 7. The requirements of Article 83 EPC are therefore not met.

6. Sufficiency of disclosure - auxiliary request 8

The invention defined in claim 1 of auxiliary request 8 differs from the invention according to claim 1 of the main request by deletion of the prevention of stroke or its recurrence and by shortening the list of active agents. These amendments have no influence on the above argumentation concerning insufficiency. As a consequence, the reasoning set out in point 3 above applies *mutatis mutandis* to the invention defined in auxiliary request 8. The requirements of Article 83 EPC are therefore not met.

7. In view of these findings, an evaluation of the further objections raised by the respondents is not necessary.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

U. Oswald