BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 7 August 2003

Case Number: T 1088/01 - 3.3.2

Application Number: 88310910.0

Publication Number: 0325843

IPC: A61K9/54

Language of the proceedings: EN

Title of invention:
Pharmaceutical formulations for preventing drug tolerance

Patentee:
ELAN CORPORATION, Plc

Opponent:
KV PHARMACEUTICAL COMPANY

Headword:
Pharmaceutical formulations/ELAN CORPORATIONS, Plc

Relevant legal provisions:
EPC Art. 54, 111(1)

Keyword:
"Novelty - yes: undisclosed feature in prior art document"
"Remittal - yes: essential issues not dealt with"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1088/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 7 August 2003

Appellant: (Proprietor of the patent)
ELAN CORPORATION, Plc
Lincoln House
Lincoln Place
Dublin 2 (IE)

Representative:
Hallybone, Huw George
Carpmaels and Ransford
43 Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 23 July 2001 revoking European patent No. 0325843 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
J. H. P. Willems

Summary of Facts and Submissions

I. European patent No. 0 325 843 based on application No. 88 310 910.0 was granted on the basis of a set of 17 claims for Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE, a set of 13 claims for Contracting State ES and a set of 15 claims for Contracting State GR.

Independent claims 1, 7, 9, 11, 15 and 16 as granted of the set of claims for the Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE read as follows:

"1. Controlled absorption ISMN containing pellet formulation for oral administration which inhibits the development of ISMN tolerance, said pellet comprising:
i) a core of
(a) a powder mixture containing an ISMN or a pharmaceutically acceptable salt thereof and optionally one or more excipients selected from an organic acid or base and a pharmaceutically acceptable diluent, and
(b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble polymer and optionally a minor proportion of a pharmaceutically acceptable water insoluble polymer,
said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core; and
(ii) a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water-insoluble polymer and

optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said membrane and the ratio of said water-soluble polymers to said water-insoluble polymers being effective to permit release of said ISMN from said pellet at a rate allowing controlled absorption thereof over a 24 hour period following oral administration, said rate being measured *in vivo* and having a Tmax between 2 and 10 hours and achieving minimum effective blood levels from 12 to 20 hours over a 24 hour period.

7. A process for the production of a controlled absorption ISMN-containing pellet according to any one of Claims 1-6, which comprises forming said core as set forth in Claim 1 and enclosing the core in a membrane of a film-forming polymer or mixture thereof as defined in Claim 1 which permits release of the ISMN or pharmaceutically acceptable salt thereof in the manner set out in Claim 1.

9. A controlled absorption ISMN formulation according to Claim 6, wherein the rapidly releasing form of ISMN comprises pellets as defined in any one of Claims 1 to 5 without said multi-layer membrane.

11. A preparation for the once-daily, percutaneous administration of ISMN or a pharmaceutically acceptable salt thereof which preparation inhibits the development of ISMN tolerance, and which comprises ISMN or a pharmaceutically acceptable salt thereof uniformly distributed in a solid, semi-solid or mucilaginous medium which can be placed in intimate contact with the skin, the release of said ISMN or pharmaceutically

acceptable salt thereof from said preparation being at a rate allowing controlled absorption thereof over a 24 hour period following topical application of said preparation, said rate being measured *in vivo* and having a Tmax between 2 and 16 hours and achieving minimum effective blood levels from 12 to 20 hours over a 24 hour period.

15. A process for the manufacture of a preparation according to any one of Claims 11-14, which comprises adding a given amount of ISMN or a pharmaceutically acceptable salt thereof to a solution of a solidifying or gel-forming agent or mixture thereof in a suitable solvent or mixture of solvents and mixing or heating the mixture thereby obtained so as to form said solid, semi-solid or mucilaginous medium.

16. Use of a drug for the manufacture of a pharmaceutical formulation for use in the once-daily administration of said drug in a method to inhibit the development of drug tolerance in humans being treated with said drug in which the once-daily formulation is adapted to achieve therapeutically effective levels of said drug in the blood over a period of not more than 20 hours of the day and further adapted to cause said blood levels to fall significantly below said therapeutic levels throughout the remainder of the 24 hour period."

II. Opposition was filed against the granted 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 Article 100(c) EPC because the claimed subject-matter contained added

matter contrary to the requirements of Article 123(2) EPC.

The following document was cited *inter alia* during the proceedings before the Opposition Division and the Board of Appeal:

(1) Pharmaceutical Research, 1985, No. 1, pages 30-36.

III. The decision of the Opposition Division pronounced on 26 April 2001 revoked the patent under Article 102(1) EPC for lack of novelty.

The Opposition Division held that the patent in suit did not meet the requirements of Article 54 EPC because document (1) disclosed in Figure 4 controlled absorption ISMN containing pellet formulations, which anticipated the subject-matter of claim 1 of the main request and of auxiliary requests 1 to 3.

IV. The appellant (patentee) lodged an appeal against the said decision.

V. With a letter dated 29 November 2001, the respondent (opponent) withdrew its opposition.

VI. With a letter dated 12 May 2003, the respondent informed the Board that it would not attend the oral proceedings.

VII. Oral proceedings were held before the Board on 7 August 2003.

During the oral proceedings, the appellant filed a main request with a set of 15 claims for Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE, a set 13 claims for Contracting State ES and a set of 13 claims for Contracting State GR.

The claims of these sets of claims correspond to the set of claims as granted, wherein claims 16 and 17 were deleted in the set of claims for Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE and wherein claims 14 and 15 were deleted in the set of claims for Contracting State GR.

Moreover, in the set of claims for Contracting States AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE, the dependency on claim "6" in claim 9 was corrected to read "8" as was the case in claim 9 of the application as originally filed.

VIII. In its view, the claimed formulation was novel over document (1) because the membrane, made of a water-insoluble polymer was not a multi-layer membrane contrary to the requirement of claim 1 of the patent in suit.

It also submitted that, whereas the pellets in the formulation according to claim 1 of the contested patent were all structurally identical, the formulation described in document (1) in fact contained two different types of pellets, namely pellets with an initial dose of ISMN (isosorbide mononitrates) coated with a water-soluble polymer and pellets with a maintenance dose of ISMN which are coated with a water-

soluble polymer plus a supplementary coating of a water-insoluble polymer.

It further argued that the disclosure in document (1) could not be regarded as novelty-destroying for the subject-matter of claim 1 of the contested patent because it was not correct to compare the computer-simulated drug release profile disclosed in Figures 3 and 4 of document (1) with the *in vivo* drug release profile of the formulations according to the patent in suit.

IX. The appellant requested that the decision under appeal be set aside and that the patent be maintained according to the main request as filed during today's oral proceedings or alternatively on the basis of auxiliary request 1 filed on 5 December 2001 or on the basis of auxiliary requests 2, 3 or 4, corresponding to auxiliary requests 1, 2 or 3, on which the decision of the Opposition Division was based.

Reasons for the Decision

1. The appeal is admissible.

2. *Formal aspects*

The Board observes that although claim 9 refers back to claim 1, it is in fact not dependent on this claim since it does not contain all its technical features, namely the multi-layer membrane (Rule 29.4 EPC).

The Board notes also that the opponent had not in fact presented any argument in support of this ground of opposition. Moreover, in its communication dated 5 February 1999 (point 4.5), the Opposition Division considered that the patent did not contain subject-matter which extended beyond the content of the application as filed.

In the cirumstances of the present case, the Board sees no reason to discuss this matter further.

3. *Novelty*

Document (1) describes the preparation of a pellet comprising

(i) a core of

(a) a mixture containing an ISMN (IS-5-N, ie isosorbide-5-nitrate) and a pharmaceutically acceptable diluent (lactose), and

(b) a polymeric material containing a major proportion of a pharmaceutically acceptable water-soluble polymer (hydroxypropylcellulose), and

(ii) a membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water-insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water-soluble polymer(9:1 ethylcellulose/polyethylene glycol) (see Materials and Methods on pages 31 and 32).

The Board observes that the part of the disclosure dealing with the preparation of the pellets recites merely that the sustained-release layer, ie the membrane (ii), was applied by the fluidised bed technique.

According to Claim 1 of the contested patent, the outside membrane (ii) must be a **multi-layer membrane**.

Moreover, as pointed out by the appellant during the oral proceedings, it is apparent for instance from Example 1 of the patent in suit that the multi-layer outside membrane is the result of a repetition of coating and curing steps.

Furthermore, in the absence of any element to the contrary, the Board has no reason to doubt that the appellant's submission made during the oral proceedings that the various layers are physically visible in the membrane is correct.

As document (1) is totally silent about such repetitions of coating and curing steps, the Board concludes that the feature of claim 1 of the patent in suit requiring that the outside membrane contain more than one layer is not anticipated by the disclosure in document (1).

The subject-matter of claim 1 is therefore novel over document (1) as required by Article 54 EPC and the decision under appeal cannot be maintained.

Accordingly, as far as the assessment of novelty is concerned, there is no need to consider the other arguments of the appellant.

The Board observes, however, that all the pellets of each of the formulations disclosed in document (1) have the same surface area (see Table 1, page 32, A(mm^2)). This fact is apparently not in agreement with the appellant's submission that the formulations described in document (1) in fact contain two different types of pellet, namely pellets with an initial dose of ISMN (isosorbide mononitrates) coated with a water-soluble polymer and pellets with a maintenance dose of ISMN which are coated with a water-soluble polymer plus a supplementary coating of a water-insoluble polymer.

In addition, whereas it is *a priori*, as a rule, correct to consider that the results of computer simulations do not anticipate *in vivo* results, such information is however highly relevant when it comes to the assessment of inventive step.

The Board notes also that the conclusions concerning the subject-matter of claim 1 cannot be extrapolated to independent claims 9, 11 and 15 which concern different subject-matter.

4. *Remittal to the first instance*

4.1 Although Article 111(1) EPC does not guarantee the parties an absolute right to have all the issues in the case considered by two instances, it is well recognised that a party should be given two opportunities to plead the important elements of a case. The essential

function of an appeal in *inter partes* proceedings is to consider whether the decision issued by the first-instance department is correct. Hence, a case is normally referred back if essential questions regarding the patentability of the claimed subject-matter have not yet been examined and decided by the department of first instance.

In particular, remittal is taken into consideration by the boards in cases where a first-instance department issues a decision solely on one particular issue which is decisive for the case against a party and leaves other essential issues outstanding. If, following appeal proceedings, the appeal on the particular issue is allowed, the case is normally remitted to the first-instance department for consideration of the undecided issues.

4.2 The above observations and comments apply fully to the present case. The Opposition Division decided that claim 1 was not patentable on the grounds of lack of novelty (Article 54 EPC), but ignored the essential issues of novelty of the other independent claims (Articles 52(1), 54 EPC) and of inventive step (Articles 52(1), 56 EPC) and sufficiency of disclosure (Article 83 EPC). These issues, however, form, *inter alia*, the basis for the requests of the respondent that the patent be revoked in its entirety and must therefore be considered as essential substantive issues in the present case.

4.3 Thus, in view of the above considerations, the Board has reached the conclusion that, in the circumstances of the present case, it is necessary to remit the case

to the Opposition Division for further prosecution on the basis of the set of claims according to the main request filed during the oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The matter is referred to the first instance for further prosecution.

The Registrar: The Chairman:

A. Townend U. Oswald