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Datasheet for the decision of 24 June 2008

Case Number: T 0421/04 - 3.3.02

Application Number: 95916264.5

Publication Number: 0719145

IPC: A61K 31/21

Language of the proceedings: EN

Title of invention:
Nitric oxide donor composition for treatment of anal disorders

Patentee:
Cellegy Pharmaceuticals, Inc.

Opponent:
Dr Falk Pharma GmbH
Norgine Pharmaceuticals Limited

Headword:
Treatment of anal disorders/CELLEGY PHARMACEUTICALS, INC.

Relevant legal provisions:
EPC Art. 123(2)

Relevant legal provisions (EPC 1973):
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Keyword:
"Article 123(2) - no: there is no basis for the amendments in the application as originally filed"

Decisions cited:
G 0001/93

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0421/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 24 June 2008

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 16 January 2004 revoking European patent No. 0719145 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
P. Mühlens

Summary of Facts and Submissions

I. European patent No. 0 719 145 based on application No. 95 916 264.5 was granted on the basis of a set of 14 claims.

The independent claims read as follows:

"1. The use of a nitric oxide donor in the manufacture of a medicament for treating an anal disease by administration of the medicament to the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of a nitric oxide donor in the manufacture of a medicament for healing anal disease by administration of the medicament to the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

3. "1. The use of a nitric oxide donor in the manufacture of a medicament for treating recurrent anal disease by administration of the medicament to the external anus and distal anal canal, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight."

II. Two oppositions were 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 for added matter over the application as originally filed.

III. The following documents were *inter alia* cited during the opposition and appeal proceedings:

(2) P.B. Loder et al., Gastroenterology 1993, 104, p. A544
(3) P.B. Loder et al., Dis. colon rectum, 1993, 36, p. 22
(4) P.B. Loder et al., Gut, 1993, 34, p. S25
(5) F. Guillemot et al., Dis. colon rectum, 1993, 36, p. 372-376
(9) M.L. Kennedy et al., Abstract CR33 of Royal Australasian College of Surgeons A.S.C., Hobart, 1-6 May 1994
(11) Slides by Dr. D. King prepared for the Sydney Colorectal Surgical Society on 17 July 1993
(15) F. Guillemot et al., Digestive Diseases and Sciences, 1992; 37(1), p. 155
(28) Declaration of Mr. J. Lund
(29) Declaration of Mr. M. Adams
(34) Declaration of Mr. D. Azarnoff

IV. In the decision pronounced on 10 December 2003, the opposition division revoked the patent. Its principal findings were as follows:

As regards the novelty of the main request, the opposition division decided that document (9) had been made publicly available before the priority date of the contested patent. Moreover, document (9) was

detrimental for the novelty of all the independent claims 1-3. In connection with the site of administration, it was held that the feature "topical application" as disclosed in document (9), which the person skilled in the art would interpret as local application at the affected area, gave a direct and unambiguous disclosure of an application to the external anus and the (distal) anal canal. The avoidance of debilitating side effects was considered to be the inevitable consequence of putting into practice the teaching of document (9).

Alternatively, if the site of administration and the avoidance of debilitating side effects could establish novelty, then the subject-matter as claimed in the main request was rendered obvious by document (9) in combination with any of documents (2) - (5) or (15). Each of the latter documents mentioned the *in situ* application of creams comprising nitroglycerin for the treatment of anal diseases. In view of the fact that the avoidance of debilitating side effects was the direct consequence of the mode of administration, this effect would automatically be obtained by the *in situ* administration.

Regarding the feature "recurrent anal diseases" of claim 3, the opposition division concluded that the introduction of this feature was not allowable under Article 123(2) EPC.

None of the auxiliary requests 1-3 could overcome the objections raised under Articles 54(2), 56 and/or 123(2) EPC in connection with the main request.

V. The patentee lodged an appeal against that decision.

VI. With the statement of the grounds of appeal dated 25 May 2004, the appellant (patentee) filed new auxiliary requests 1 - 5. The independent claims read as follows:

a) Auxiliary request 1:

" 1. The use of a nitric oxide donor in the manufacture of a medicament for treating an anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of a nitric oxide donor in the manufacture of a medicament for healing anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

3. The use of a nitric oxide donor in the manufacture of a medicament for treating recurrent anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to the external anus and distal anal canal,

wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight."

b) Auxiliary request 2:
" 1. The use of a nitric oxide donor in the manufacture of a medicament for treating an anal disease by administration of the medicament to or proximate the affected area in the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of a nitric oxide donor in the manufacture of a medicament for healing anal disease by administration of the medicament to or proximate the affected area in the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight."

c) Auxiliary request 3:
"1. The use of a nitric oxide donor in the manufacture of a medicament for treating an anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of a nitric oxide donor in the manufacture of a medicament for healing anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight."

d) Auxiliary request 4:

" 1. The use of nitroglycerine in the manufacture of a medicament for treating an anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitroglycerine is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of nitroglycerine in the manufacture of a medicament for healing anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitroglycerine is present in the medicament in an amount from 0.01 to 0.5% by weight."

e) Auxiliary request 5:

" 1. The use of nitroglycerine in the manufacture of an ointment medicament for treating an anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the external anus and distal anal canal so as to provide relief of pain associated with said disease whilst avoiding debilitating side effects, wherein the nitroglycerine is present in the medicament in an amount from 0.01 to 0.5% by weight.

2. The use of nitroglycerine in the manufacture of an ointment medicament for healing anal disease selected from anal fissure, anal ulcer, haemorrhoidal disease and levator spasm by administration of the medicament to or proximate the affected area in the anal canal so as to provide relief of pain associated with said disease without debilitating side effects, wherein the nitroglycerine is present in the medicament in an amount from 0.01 to 0.5% by weight."

VII. The appellant's arguments can be summarised as follows:

a) Errors of law and procedure:

It was held that the following errors of law and procedure were made by the opposition division:

1) There was a gross inconsistency between the minutes of the oral proceedings and the decision in connection with the upper limit of the concentration range of the nitric oxide donor, i.e. 0.5%. According to paragraph 12 of the

minutes, this feature did not appear to make a technical contribution to the invention, so that according to decision G 01/93 (OJ EPO 1994, 541), it could be allowed. The decision under appeal, however, contained no such finding. On the contrary: it was even mentioned in the decision that there was no apparent basis in the original application for this feature in relation to nitric oxide donors.

2) Although the appellant had cited decision G 01/93 only in connection with the concentration of 0.5%, the opposition division considered it necessary in view of G 01/93 to discuss novelty and inventive step in order to establish the relevance of the link between administration to the affected area and the avoidance of debilitating side effects, thereby disregarding the reasoning of the appellant. Moreover, instead of analysing whether the particular features in question made a technical contribution, the opposition division examined whether they contributed to the novelty and inventive step, thereby profoundly misinterpreting decision G 01/93.

3) In its decision, the opposition division disregarded evidence submitted by the appellant. In particular, documents (28) and (34) were not taken into consideration.

4) Although the opposition division had decided that document (11) did not belong to the state of the art, the teaching of document (9) was interpreted in the light of document (11).

b) Article 123(2) EPC:

In connection with the nitric oxide donor concentration of 0.5%, it was held that, since the original application taught the use of concentrations which greatly exceeded 0.5%, the introduction of this feature did not make a technical contribution to the claimed invention, but was merely an arbitrary limitation which was allowable under Article 123(2) EPC in view of G 01/93.

Alternatively, it was argued that the nitric oxide donor concentration of 0.5% was specifically disclosed in the original application. In this context, reference was made to declarations (28) and (29).

VIII. The relevant arguments of respondent 2 can be summarised as follows:

Respondent 2 held that the opposition division had not committed any errors of law and procedure. In addition, it was argued that none of the requests on file was allowable under Article 123(2) EPC, as there was no basis in the application as originally filed for the upper concentration limit of 0.5% of the nitric oxide donor, or more specifically, of nitroglycerine.

IX. The appellant had requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the claims granted or, alternatively, any one of auxiliary requests 1-5 filed with the statement of the grounds of appeal dated

25 May 2004. Respondent 2 had requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Remittal to the first instance*

None of the alleged errors and failures of the opposition division amounts to a procedural violation, nor can the Board see a failure to respect the patentee's right to be heard. Alleged wrong conclusions in a decision do not constitute procedural violations. Moreover, the board holds that the case was discussed at length before the opposition division, in writing and in the oral proceedings. Thus, the appellant had ample opportunities to present his case properly. The fact that the opposition division came to different conclusions is, again, not a procedural point.

3. *Main request*

3.1 Amendments before grant (Articles 100(c) and 123(2) EPC):

Claim 1 relates to the use of a nitric oxide donor in the manufacture of a medicament for…, wherein the nitric oxide donor is present in the medicament in an amount from 0.01 to 0.5% by weight.

3.1.1 Basis for the feature 0.5% by weight in the original application:

There is no disclosure of this feature in the general part of the description or in the claims of the original application. Example 1, however, discloses a nitroglycerin ointment, comprising 0.5 % nitroglycerin in a mixture comprising white petrolatum, lanolin and distilled water. In subsequent examples, this ointment is used in the treatment of posterior midline anal fissure (example 5), superficial posterior midline anal fissure (example 6), levator spasm (example 11), acutely thrombosed external hemorrhoids as well as anal fissures or ulcers (example 12).

In connection with the composition of the medicament, the achievement of the desired therapeutic effect as well as the avoidance of debilitating side effects as claimed in present claim 1 depend, among others, on the following factors:
a) type of active agent
b) concentration of the active agent
c) composition of the vehicle in which the active agent is formulated.

As each of these factors contributes to the overall performance of the medicament, the following consequence has to be drawn: the fact that an ointment comprising 0.5% by weight of nitroglycerin in the specific vehicle of example 1 achieves the desired effects whilst avoiding debilitating side effects does not allow the conclusion that the same effects are also obtainable with a medicament comprising 0.5% of the same or of a different nitric oxide donor **in a**

different vehicle. Example 1 can therefore not serve as the basis for the concentration of 0.5% by weight of a nitric oxide donor in a non-specified vehicle as presently claimed.

It is noted that examples 2-4 of the original application also disclose specific ointments comprising 0.5% by weight of nitroglycerin in specific vehicles which, like the vehicle in example 1, are also based on diluted nitroglycerin ointment, USP 2%. As a consequence, the reasoning of the paragraph above in connection with example 1 also applies to examples 2-4. Moreover, the compositions of these examples additionally comprise a second active agent, namely 1% hydrocortisone (example 2) or 0.5% dibucaine (examples 3 and 4). These mixtures of active agents are even less suitable as a basis for claim 1 than the composition of example 1, as the subject-matter claimed therein includes the use of compositions comprising 0.5% by weight of a nitric oxide donor as the sole active agent.

3.1.2 Technical contribution of the upper concentration limit of 0.5% by weight:

The fact that the original application includes the use of concentrations of nitric oxide donors which greatly exceed 0.5% does not mean that the introduction of this upper concentration limit does not make a technical contribution to the claimed invention. On the contrary: any change in the concentration of an active agent has an impact on the intensity of its pharmacological effect as well as of its side effects. Therefore, any amendment to the concentration ranges of the active

agent modifies its performance and thus makes a technical contribution. As a consequence, the amendment is not allowable in view of decision G 01/93 either.

3.1.3 Further arguments by the appellant:

In connection with the basis for the nitric oxide donor concentration of 0.5% in the original application, the appellant referred to declarations (28) and (29). In these declarations, it was essentially argued that in view of the fact that the original application generally disclosed concentration ranges from 0.01 to 10% or from 0.01 to 4%, intermediate ranges such as 0.01 to 0.5% would also work and were intended to be used for any nitric acid donor in any vehicle.

However, this argument does not hold for the following reasons: amendments are only allowable under Article 123(2) EPC, if they are specifically disclosed in the original application, either by explicit or implicit disclosure. As in the present case the feature in question was only disclosed in working examples, it had to be examined whether or not these examples could be generalised in the light of the entire content of the original application. In this context, the board notes that the original application does not appear to contain any information as to the circumstances, under which the debilitating side effects can be avoided (see claims 1-3, where the avoidance of debilitating side effects is part of the claimed use). The avoidance of debilitating side effects is disclosed on page 6, lines 4-10 of the original application. Later on, in lines 25-26 of the same page, this disclosure is relativised by the statement that "**in many patients**

treatment can be obtained without debilitating side effects" [emphasis added by the board], which means that there are situations in which these unwanted effects cannot be avoided. Apart from the patient's individual constitution and the concentration of the active agent - it stands to reason that debilitating side effects can most effectively be avoided at the lower end of the concentration range - the presence or absence of debilitating side effects may also be dependent on other factors including the release rate which in its turn **depends on the vehicle** in which the active agent is embedded. Therefore, as was already pointed out in paragraph 3.1.1 above, there is no disclosure in the original application that the desired effects and the avoidance of debilitating side effects can be achieved with a medicament comprising 0.5% of a nitric oxide donor such as nitroglycerine in a vehicle which is different from those used in the examples. As a consequence, example 1 (and examples 2-4) cannot be generalised.

3.1.4 Therefore, the subject-matter of claim 1 does not meet the requirements of Article 123(2) EPC.

3.1.5 For the same reasons as outlined in paragraphs 3.1.1 to 3.1.3, the subject-matter of claims 2 and 3 does not meet the requirements of Article 123(2) EPC either.

3.2 In the light of this finding, it is not necessary to examine the further objections raised under Article 100(c) and 123(2) EPC as well as the objections raised under Articles 54, 56 and 83 EPC.

4. *Auxiliary requests 1-4:*

With regard to the independent claims of auxiliary requests 1-4, it is emphasised that the galenic form of the composition is not defined at all: it therefore includes ointments as in examples 1-4, but also comprises quite different forms such as suppositories or fluids. As the board arrived at the conclusion that example 1 as well as examples 2-4 do not provide a basis for a claim pertaining to the use of a composition comprising a nitric acid donor such as nitroglycerin and a vehicle which is structurally different from the vehicle of the said examples, the reasoning developed in paragraph 3.1.1 to 3.1.3 in connection with the main request fully applies to the independent claims of auxiliary requests 1-4.

5. *Auxiliary request 5:*

As for auxiliary request 5, it is noted that the compositions are now limited to ointments. However, even within the group of ointments, there exists a wide spectrum of possible formulations. Ointments may be hydrophilic or hydrophobic, they may are may not contain penetration enhancers or other adjuvants, they may be highly or less highly viscous, etc. Each of these factors influences the intensity of the therapeutic effects and of the unwanted side effects. Therefore, the reasoning developed in paragraph 3.1.1 to 3.1.3 in connection with the main request also applies to the independent claims of auxiliary request 5 despite the limitation to ointment formulations. As a consequence, examples 1 and 2-4 cannot serve as the basis for the upper concentration limit of 0.5% by

weight of nitroglycerine in independent claims 1 and 2 of auxiliary request 5 either.

6. As none of the requests on file meets the requirements of Article 123 EPC, a discussion of the further objections raised in connection with Article 54, 56 and 83 EPC is not necessary.

7. *Reimbursement of the appeal fee:*

According to Rule 103(1)a) EPC, the appeal fee shall be reimbursed if the board of appeal deems an appeal to be allowable, and if such reimbursement is equitable by reason of a substantial procedural violation. In the present case, the appeal has been found to be not allowable. Consequently, the request for reimbursement of the appeal fee has to be refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald