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Datasheet for the decision of 22 July 2010

Case Number: T 1724/07 - 3.3.02

Application Number: 98938896.2

Publication Number: 1008341

IPC: A61K 9/08

Language of the proceedings: EN

Title of invention:
Glucose-containing preparation

Patentee:
Shimizu Pharmaceutical Co., Ltd.

Opponent:
Gambro Lundia AB

Headword:
Glucose-Containing Preparation/SHIMIZU PHARMACEUTICAL CO., LTD

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
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Keyword:
"Inventive step - (no): the comparative tests do not show an improvement over the closest prior art"
"Reformulation of the problem,, obvious alternative"

Decisions cited:
-

Catchword:
-

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Case Number: T 1724/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 22 July 2010

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 6 August 2007 concerning maintenance of European patent No. 1008341 in amended form.

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
J.-P. Seitz

Summary of Facts and Submissions

I. European patent No. 1 008 341 based on application No. 98 938 896.2 was granted on the basis of a set of 6 claims.

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of inventive step and under Article 100(c) EPC for amendments that contain subject-matter extending beyond the content of the application as originally filed.

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

(1) English translation of JP-A-09-87182
(2) WO 93/19792
(3) Peritoneal Dialysis International, vol. 17, no. 1, 9-10 (1997)
(4) Peritoneal Dialysis International, vol. 17, no. 1, 27-34 (1997)
(5) Peritoneal Dialysis International, vol. 16, no. 5, 444-445 (1996)
(6) Peritoneal Dialysis International, vol. 17, no. 1, 42-47 (1997)
(12) Experimental data filed by the appellant with letter dated 4 October 2006
(13) Comparative data filed by the respondent with letter dated 16 May 2001

IV. The present appeal lies from an interlocutory decision of the opposition division dated 19 June 2007 maintaining the patent in amended form on the basis of the auxiliary request filed with letter of 18 May 2007.

The independent claims of the auxiliary request read as follows:

"1. A glucose-containing preparation comprising separately housed first and second solutions, said first and second solutions satisfying the following conditions:

(a) the first solution

— contains 2-50% glucose;

— is obtainable by pH adjustment to 3-5 with a lactic acid-sodium lactate or an acetic acid-sodium acetate buffer solution; and

— contains

0.7 or 1.0 mEq/L of lactic acid together with 0.2 mEq/L of sodium lactate; or

0.3 or 0.4 or 0.6 or 0.7 or 0.8 or 0.9 or 1.0 mEq/L of lactic acid together with 0.3 mEq/L of sodium lactate;

or

0.3 mEq/L of lactic acid together with 1.0 mEq/L of sodium lactate; or

0.3 mEq/L of acetic acid together with 1.0 mEq/L of sodium acetate; or

1.0 mEq/L of acetic acid together with 0.3 mEq/L of sodium acetate;

(b) a second solution contains an alkalizing agent, and has a pH value of 8-13 as a pH adjustor for said first solution; and

(c) the glucose concentration is 1-15% in the preparation solution obtained by mixing the first solution and second solution, and the pH of the solution is in a range of 6-8.

6. A perfusate preparation suitable for CAPD comprising separately housed first and second solutions, said first and second solutions being such that the first solution

- contains 2-50% glucose;
- is obtainable by pH adjustment to 3-5 with a lactic acid-sodium lactate or an acetic acid-sodium acetate buffer solution; and
- contains
  0.7 or 1.0 mEq/L of lactic acid together with 0.2 mEq/L of sodium lactate; or
  0.3 or 0.4 or 0.6 or 0.7 or 0.8 or 0.9 or 1.0 mEq/L of lactic acid together with 0.3 mEq/L of sodium lactate; or
  0.3 mEq/L of lactic acid together with 1.0 mEq/L of sodium lactate; or
  0.3 mEq/L of acetic acid together with 1.0 mEq/L of sodium acetate; or
  1.0 mEq/L of acetic acid together with 0.3 mEq/L of sodium acetate;

the second solution contains sodium lactate as an alkalizing agent and has a pH value of 8-13 as a pH adjustor for said first solution, and the glucose concentration is 1-15% in the preparation solution obtained by mixing the first solution and second solution, the pH of the solution being in a range of 6-8."

V. As regards the main request, filed with letter of 7 November 2005, the opposition division came to the conclusion that the subject-matter claimed therein did not meet the requirements of Article 123(2) EPC.

As regards the subject-matter of the auxiliary request, the opposition division decided that the requirements of Article 123(2) EPC were met. It came to the conclusion that it was not necessary to include the specific glucose concentrations of the examples into present claim 1, as there was a general disclosure of a glucose concentration of 2 to 50% in the description of the original application. The examples, which constituted preferred embodiments of the invention, were assumed to be within this range.

As for inventive step, the opposition division considered document (1), which disclosed glucose-containing dialysis solutions, in which lactic acid and sodium lactate concentrations were significantly higher, to be the closest prior art. The problem to be solved with respect to document (1) was defined as the provision of a glucose-containing dialysis solution containing a lower amount of the by-product formic acid. The solution proposed in present claims 1 and 6 was not obvious, as there was no indication in the available prior art about the effect of low sodium lactate/lactic acid concentrations on the stability and formic acid concentration of glucose-containing dialysis solutions. According to the opposition division, it was plausible to extend the beneficial effects shown for sodium lactate/lactic acid to the system sodium acetate/acetic acid.

VI. The appellant (opponent) lodged an appeal against that decision.

VII. Oral proceedings were held before the board on 22 July 2010.

VIII. In connection with inventive step, the appellant argued that the opposition division had erred in defining the technical problem vis-à-vis document (1) (= closest state of the art) as "provision of a glucose-containing dialysis solution with lower amount of by-production of formic acid" for the following reasons: firstly, formic acid concentration was not the best indicator for cell toxicity; secondly, the patentee had failed to provide evidence in support of such an amelioration. Document (13) constituted the only evidence in support of an improvement over the teaching of document (1). However, the comparative tests described therein were flawed for several reasons. To begin with, the compositions allegedly representing the claimed invention were no longer encompassed by the subject-matter of the claims. Moreover the comparison had not been made with the closest prior art (document (1)) but with products according to document (2). In the absence of any evidence in support of an improvement, the problem vis-à-vis document (1) merely consisted in the provision of an alternative preparation for peritoneal perfusion, which was solved by reducing the buffer concentration. That solution was obvious, as the skilled person had an interest in taking minimum concentrations of the constituents for purely economic reasons. Moreover, the teachings of documents (3) to (6), which recognised that high levels of lactic acid buffer were harmful, would lead the skilled person to use lower buffer concentrations.

IX. In connection with inventive step, the respondent, starting from document (1) as closest prior art, defined the problem to be solved as the provision of a glucose- containing dialysis solution with a lower amount of by-production of formic acid. He held that the burden of proof was on the opponent (appellant), who had failed to show that the problem defined above had not been solved. Although the compositions used in the comparative tests of document (13) were not encompassed by the subject-matter of the claims and had not been compared with the closest state of the art, these tests nevertheless led to the conclusion that the above-mentioned problem had been plausibly solved.

X. The appellant requested that the decision under appeal be set aside and that the European patent No. 1008341 be revoked.

XI. The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Sole request - inventive step of claim 1:

2.1 The present invention concerns the provision of glucose- containing peritoneal perfusates in the form of separately housed first and second solutions, in which degradation of glucose is minimised (see paragraphs [0015] and [0016] of the contested patent).

Document (1), which is concerned with the same problem, constitutes the closest prior art. Example 1 discloses a peritoneal perfusate in which the first solution comprises 5.0 g/dl glucose, 123.8 mM NaCl, 1.875 mM $CaCl_2$, 0.3125 mM $MgCl_2$, 28.75 mM sodium lactate and 2.5 mM lactic acid. The pH of the first solution was calculated to be 4.8. The second solution contains an alkalizing agent so that the final solution, which is obtained by combining the first and second solutions, has a pH of 7.0 and a glucose concentration in the range of 1-15%.

2.2 For defining the technical problem vis-à-vis document (1), and in particular for determining whether or not the subject-matter as defined in present claim 1 constitutes an improvement, the following point has to be taken into consideration: if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the said effect is convincingly shown to have its origin in the distinguishing feature of the invention. According to the established jurisprudence, alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem to be solved.

2.3 In the present case, the respondent submitted document (13) in order to show that the perfusates according to the contested patent were more stable and contained less glucose degradation products, in particular formic acid, than the compositions of the state of the art. However, these comparative tests are deficient for the following reasons:

(a) The compositions of document (13) are not encompassed by the subject-matter defined by the claims: compositions S1, S2 and S3, which are supposed to constitute compositions of the present invention, are characterised by lactic acid concentrations of 0.02 mEq/L, 0.06 mEq/L and 1.9 mEq/L, whereas the lactic acid concentration of the preparations according to the claims is between 0.3 mEq/L and 1.0 mEq/L.

(b) In view of the fact that the compositions D1, D2 and D3 are representative of document (2) instead of document (1), the comparison was not made with the closest state of the art.

(c) The comparative tests do not convincingly show that the improvement is caused by the distinguishing feature, i.e. the reduced buffer level, as there are numerous differences between S1, S2 and S3 on the one hand and D1, D2 and D3 on the other. Apart from the buffer level, these differences include in particular the electrolyte composition: S1, S2 and S3 contain 3.5 mmol/L of $CaCl_2 \cdot 2H_2O$, whereas D1, D2 and D3 comprise 4.7 mmol/L of $CaCl_2 \cdot 2H_2O$, 2 mmol/L of $MgCl_2 \cdot 6H_2O$ and 258 mmol/L of NaCl.

2.4 As regards point (a) above, the respondent held that although the lactic acid concentrations in document (13) were both below and above and therefore outside the concentrations as claimed, there was no reason to believe that the concentrations within these extremes would yield a different effect. As a consequence,

document (13) nevertheless demonstrated a reduced by-production of formic acid for the compositions as defined in the present claims. This argument cannot be followed, as there is no evidence for a linear relationship between by-production of formic acid and buffer concentration. It can therefore not be excluded that lactic acid concentrations within the range of 0.06-1.9 mE/L are characterised by an enhanced by-production of formic acid.

In connection with point (c) above, the respondent held that the buffer levels constituted the main difference in the comparative tests. Despite additional marginal variations in the constitution of the compositions, the different buffer levels provided therefore the only plausible explanation for the shown effect. Again, the board is not able to follow this argumentation for the reasons outlined in point 2.2 above.

2.5 As a consequence, document (13) does not demonstrate an improvement in terms of a reduced formation of formic acid by the claimed subject-matter over the closest state of the art.

2.6 The same applies to enclosure 3, filed by the appellant with the statement of the grounds of appeal dated 6 December 2007. The respondent reasoned that the comparison between samples B and D of enclosure 3, which correspond to samples 3 and 8 of document (12), proved that a reduction of the lactic acid/sodium lactate buffer concentration yielded lower formic acid levels. However, samples B and D do not only differ in the buffer level. Sample B comprises 8% glucose and 1 mM lactate, wherein the pH is adjusted to pH 5 by

adding 1 mM lactic acid. In contrast thereto, sample D contains 8% glucose, 40 mM lactate, 4.7 mM $CaCl_2$, 2 mM $MgCl_2$ and 258 mM NaCl, wherein the pH is adjusted to pH 5 by adding 1 M HCl. In view of the numerous differences between samples B and D, it was again not shown that the reduction of the formic acid level is due to the distinguishing feature of present claim 1 (see paragraph 2.3(c) above). Moreover, in view of the fact that sample D of enclosure 3 is not representative of document (1), there is again no comparison with the closest state of the art (see paragraph 2.3(b) above).

2.7 In the absence of any evidence for an improvement vis-à-vis the closest state of the art, the problem underlying the present invention can be seen as the provision of a further glucose containing peritoneal perfusate. The problem was solved by the compositions as defined in claim 1, where the lactic acid and sodium lactate are used in specific concentrations or where the lactic acid/sodium lactate buffer is replaced by specific levels of the buffer system acetic acid/sodium acetate. In view of the test examples of the contested patent, the board is convinced that the problem has been plausibly solved.

The first solutions of present claim 1 are characterised by lower lactic acid/sodium lactate levels as compared to example 1 of document (1). However, the skilled person, starting from the teaching of document (1), had a clear incentive to reduce the lactic acid/sodium lactate levels, as there are strong indications in the state of the art that high amounts of this buffer system are harmful in terms of biocompatibility (see document (3), first paragraph in

the second column of page 9 and document (5), second complete paragraph in the second column of page 444). In the light of this teaching, the skilled person would therefore reduce the lactic acid/sodium lactate levels in the first solution.

The respondent reasoned that documents (3) and (5) were not pertinent, as the biocompatibility problems mentioned above concerned the final rather than the first solution. This argument cannot be followed, as the acidic lactic acid/sodium lactate buffer is added only to the first solution. Therefore, reduction of the lactic acid/sodium lactate levels in the first solution is an adequate means for reducing these levels in the final solution.

In the absence of any further non-obvious effects, the subject-matter as claimed in the sole request therefore does not meet the requirements of Article 56 EPC.

3. In view of the above findings, an evaluation of the ground of opposition according to Article 100(c) EPC is not necessary.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin J. Riolo