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**D E C I S I O N**  
**of 9 January 2001**

**Case Number:** T 0911/95 - 3.3.4

**Application Number:** 86905335.5

**Publication Number:** 0270545

**IPC:** A61K 37/18

**Language of the proceedings:** EN

**Title of invention:**  
Medicinal composition

**Patentee:**  
3i Research Exploitation Limited

**Opponent:**  
Baxter International Inc.

**Headword:**  
Medicinal composition/3i RESEARCH

**Relevant legal provisions:**  
EPC Art. 123(2), 123(3), 56

**Keyword:**  
"Added subject-matter (no)"  
"Extension of scope (no)"  
"Inventive step (no)"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0911/95 - 3.3.4

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.4**  
**of 9 January 2001**

**Appellant:** Baxter International Inc.  
(Opponent) One Baxter Parkway  
Deerfield, Ill. 60015-4633 (US)

**Representative:** Mr. I. Dee  
Eric Potter Clarkson  
Park View House  
58 The Ropewalk  
Nottingham NG1 5DD (GB)

**Respondent:** 3i Research Exploitation Limited  
(Proprietor of the patent) 91 Waterloo Road  
London SE1 8XP (GB)

**Representative:** Eyles, Christopher Thomas  
W. P. Thompson & Co.  
Celcon House  
289-293 High Holborn  
London WC1V 7HU (GB)

**Decision under appeal:** Interlocutory decision of the Opposition Division  
of the European Patent Office posted 19 October  
1995 concerning maintenance of European patent  
No. 0 270 545 in amended form.

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey  
**Members:** A. L. L. Marie  
S. C. Perryman

## Summary of Facts and Submissions

I. European Patent No. 0 270 545, with the title "Medicinal composition" was granted on the basis of the following set of claims:

"1. A dialysis fluid comprising an aqueous solution containing as an osmotic agent a peptide containing hydrolysate of milk protein."

"2. A dialysis fluid as claimed in claim 1 in which the protein is sodium caseinate."

"3. A dialysis fluid as claimed in claim 1 or claim 2 in which the hydrolysate is prepared by enzymic hydrolysis of the milk protein with a proteolytic enzyme."

"4. A dialysis fluid as claimed in claim 3, in which the proteolytic enzyme is trypsin, chymotrypsin, pancreatin, pronase or mixtures thereof."

"5. A dialysis fluid as claimed in any preceding claim, having osmolality of from 100 to 400 mOsm/Kg."

"6. A dialysis fluid as claimed in claim 5, in which the osmolality is substantially 300 mOsm/Kg."

"7. A dialysis fluid as claimed in any preceding claim, in which the said aqueous solution has a pH of 6.6."

"8. A dialysis fluid as claimed in any preceding claim, in which the said aqueous solution contains physiological amounts of one or more of sodium, calcium, chloride, lactate, citrate and magnesium

ions."

II. Its patentability was challenged by the opponent in view of Article 100(a) EPC for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC). This resulted in its maintenance by the opposition division on the basis of an amended set of 7 claims, claim 1 of which read:

"1. The use of a mixture of peptides, which is a hydrolysate of milk protein, in the manufacture of a medical dialysis fluid comprising an aqueous solution containing an osmotic agent and physiological amounts of one or more of sodium, calcium, chloride, lactate, citrate and magnesium ions, the mixture of peptides acting as said osmotic agent."

Claims 2 to 7 being the same as the claims as granted, except for the "use-claim" format.

III. The appeal of the opponent lies against this interlocutory decision by the opposition division.

IV. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the boards of appeal giving the Board's preliminary, non-binding opinion.

V. Oral proceedings were held on 9 January 2001.

VI. During the oral proceedings, the respondent introduced as a main request the following set of 3 claims:

"1. The use of a mixture of peptides, which is an enzymic hydrolysate of sodium caseinate, in the

manufacture of a medical dialysis fluid comprising an aqueous solution having a pH of 6.6, containing an osmotic agent and physiological amounts of one or more of sodium, calcium, chloride, lactate, citrate and magnesium ions, the mixture of peptides prepared by enzymic hydrolysis of the milk protein with a proteolytic enzyme selected from trypsin, chymotrypsin or mixtures thereof and acting as said osmotic agent."

"2. The use as claimed in any preceding claim, the fluid having an osmolality of from 100 to 400 mOsm/Kg."

"3. The use as claimed in claim 2, in which the osmolality is substantially 300 mOsm/Kg."

VII. Among all the documents relied on by the appellant and the respondent during the appeal procedure, the following ones are cited in this decision:

- (1) US-4 339 433;
- (2) Handbook of Chemistry and Molecular Biology, 3rd. edition, G.D. Fasman ed. , CRC Press, Cleveland, Ohio, 1976, pages 505-508;
- (3) WO 82/03987;
- (4) CA-1039562;
- (5) US-4 495 176;
- (6) US-4 427 658;
- (7) US-4 462 990;

- (8) L. D. Stegink et al., The Journal of Pediatrics, 1971, Vol. 78, No. 4, pages 595-602;
- (9) The United States Pharmacopeia, The National Formulary, published 1980, Official Monographs/Protein, pages 687-688;
- (10) WO 82/03773;
- (11) The Merck Index, 1983, 10th edition, page 1136;
- (13) H.N. Christensen et al., The Journal of Biological Chemistry, 1946, Vol. 166, pages 649-652;
- (14) R. Stasna et al., Nutr. Metab., 1979, Vol. 23, pages 349-356;
- (15) DE-2817144.

VIII. The arguments presented by the appellant in writing and during the oral proceedings relevant to the main request are summarized as follows:

**Clarity:**

The use in claim 1 of "...comprising..." and of the undetermined pronoun "...an..." in the expression "...an osmotic agent..." as well as the absence of a precise definition of the enzymic hydrolysis conditions were considered as rendering the scope of the claims unclear and susceptible to have a possible impact on the assessment of novelty and/or inventive step.

**Novelty:**

It was considered that document (3) disclosed all the technical features of claim 1.

***Inventive step:***

Three lines of argumentation were followed using documents (1), (3) and (10), which all concerned the problem of avoiding the drawbacks related to the use of glucose or carbohydrates as an osmotic agent in dialysis fluids.

Document (3) solved this problem by using a mixture of glycerol and an amino acid source material, such as those already used in parenteral nutrition, which can contain a peptide hydrolysate derived from casein. The use of glycerol nevertheless presenting some disadvantages, the technical problem to be solved was seen in the preparation of a dialysis fluid without glycerol, but still offering good dialysis conditions. The solution was to bring the teachings of document (3) to their logical end and replace the glycerol as an osmotic agent by the amino acid source material, such as the known solutions for parenteral nutrition (documents (8), (13), (14)).

Document (10) used glucose and a mixture of amino acids as osmotic agents and insulin to favour the assimilation of both components by the human body. The mixture of amino acids, being used to at least partly replace the glucose, could also contain short-chain peptides and reference was made on page 6, lines 22 to 24 to already available mixtures for parenteral nutrition, such as those known from documents (8), (13) and/or (14). The technical problem to be solved was similar to that of document (3), ie avoiding the use of glucose, while maintaining the necessary osmotic pressure. The complete replacement by the mixture of amino acids was seen as a straightforward solution to this.

Confronted with the same problem, document (1) used, among other possibilities, polypeptides and/or proteins containing at least 10 mole percent of peptide units selected from the group consisting of aspartic acid, glutamic acid or combination thereof. Casein fell within this definition according to document (2), and was an obvious choice since document (1) suggested looking to the food industry (documents (4)-(6)) to find appropriate amino acid source material. Document (1) disclosed peptides with a length of 9-10 amino acid residues, which, in view of documents (3), (8), (10), (13) and (14) would have obviously been prepared by enzymic hydrolysis.

IX. The arguments of the respondent relevant to the main request can be summarized as follows:

**Clarity:**

The patent demonstrated without any ambiguity that an enzymatic hydrolysate obtained from milk protein can be used as the sole osmotic agent in a peritoneal dialysis fluid.

**Novelty:**

Contrary to the dialysis fluid of the patent in suit, that of document (3) contained, besides the amino acid source material, glycerol as an osmotic agent. The amino acid source material principally acted as a nutrient and not as an osmotic agent, partly because of its cost (page 6, lines 6 to 15). This implied that said amino acid source material had to be composed of free amino acids or short-chain peptides, so that it rapidly crossed the peritoneal membrane as in the case of *Amigen* described in documents (8) and (13) or of the unidentified casein hydrolysate of document (14). This



led to the assumption that said amino acid source material had been obtained by chemical hydrolysis.

***Inventive step:***

As far as document (3) was concerned, the use of casein hydrolysates as an osmotic agent would not have been obvious for the skilled man, since they had previously only been used as a nutrient. This use requiring size properties which were opposite to that of an osmotic agent.

Furthermore, the statement on page 652 of document (13) (implicitly referred to in document (3)) that the peptides of *Amigen* were more poorly retained by the kidneys than were the free amino acids would have taught away from the solution of the patent in suit.

The title of document (10) demonstrated that glucose was sought to be a constituent of the dialysis fluid. It was a speculative document, since no example was given. The same arguments exposed in relation to the amino acid source of document (3) were repeated. Document (10) appeared to be concerned with a modified glucose-containing dialysis fluid for use by diabetics and did not disclose or even suggest a dialysis fluid wherein the whole glucose has been replaced by an amino acid source material, since on page 4, lines 14 to 15 reference was made to "...less sugar...".

Document (1) had nothing to do with casein and enzymic hydrolysis, but referred to proteins or to synthetic polypeptides (col. 5, lines 34 to 39) with high molecular weights as could have been deduced from the examples using dextran (PM: 5,000 and 40,000), sodium poly(ethylene maleate)(PM: 8,000) and/or succinylated

gelatin (PM: 35,000). This could have led to solubility problems, since an important amount of protein was necessary to achieve the required osmotic pressure. Confirmation of this assumption was seen in the fact that the succinylated gelatin was used, the function of the succinylation being to introduce negative charges in the molecule and hence increase its solubility.

- X. The appellant requested that the decision under appeal be set aside and the patent be revoked.
  
- XI. The respondent, having withdrawn all other requests, requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request submitted at the oral proceedings on 9 January 2001.

## **Reasons for the Decision**

### *Article 54 EPC.*

- 1. The appellant has raised novelty objections (Article 54 EPC) in the light of the ambiguity of claim 1 (Article 84 EPC) and the Board acknowledges their possible relevance. However, in the light of the Board's conclusions on the fulfilment of the requirements of Article 56 EPC (see below), the Board does not deal with this issue.

### *Article 56 EPC*

- 2. The appellant (cf. section VII) considered each of the documents (1), (3) and (10) as being a suitable closest prior art and defined the technical problem to be

solved by the patent in suit in view of each of these documents, hence following three lines of argumentation.

3. The Board does not share this view and favours document (1) as the closest prior art. Document (1) is concerned with a dialysis fluid for CAPD (continuous ambulant peritoneal dialysis) and the disadvantages related to the use of glucose as an osmotic agent. It offers, among other solutions to this problem, the use as the sole or primary osmotic agent of a peptidic substance, which is defined as being a polypeptide or a protein containing at least 10 mole percent of peptide units selected from the group of aspartic acid and glutamic acid or combination thereof. Document (1) is therefore in the same technical field as the patent in suit, is directed to the same effect or purpose and appears closer to the patent in suit as far as it uses only a peptidic substance as an osmotic agent.
4. On the contrary, document (3), besides an amino acid source material, still uses glycerol, a molecule, which, because of its low molecular weight, is rather unsuitable for establishing a stable, long-lasting osmotic pressure as required by CAPD and the rationale behind the solution proposed by document (10), which uses glucose and an amino acid material source as osmotic agent, appears quite different from that of the patent in suit, since said solution, ie use of insulin, does not aim at avoiding the osmotic agent to cross the peritoneal membrane, as in the patent in suit, but becomes effective only after said substance has crossed the peritoneal membrane.
5. The technical problem to be solved in view of

document (1) can be formulated as the adaptation of the teachings of document (1) to provide an efficient and safe dialysis fluid fulfilling the requirements of CAPD.

6. The solution to this problem is represented by the objects defined in the claims of the main request.
7. Claim 1 of the main request of the patent in suit differs from document (1) by the mention of a pH value of 6.6, of physiological salts, of caseinate and of enzymic hydrolysis using the listed proteases.
8. It has to be determined, in relation to inventive step, whether these specific features (caseinate, pH 6.6, enzymic hydrolysis, physiological salts) are suggested in the closest prior art document and/or other documents, the teachings of which could be combined therewith, and/or in the common general knowledge of the skilled man. Of course, this has to be done in the context of CAPD, which as a long-lasting process requires, according to the well-known considerations of physics behind the dialysis/osmosis phenomenon, that the osmotic agent should not cross the (peritoneal) membrane during its completion. The fulfilment of this requirement implies that the osmotic agent must be of a rather high molecular weight. However, this requirement comes in conflict with another well-known consideration of physics, according to which the osmotic pressure, in a first approximation, is a function of the concentration of the dissolved osmotic agent, thus suggesting a rather low molecular weight. These opposite requirements may result in the fact that before the useful concentration is reached the osmotic agent becomes insoluble.

9. The first question to be answered concerns the motivation of the skilled man to use the "peptidic-route" preferentially to the other possibilities mentioned in document (1). The Board considers that the skilled man would have preferentially followed this "route", because there was a trend in the prior art in favour of the use of peptidic substances as osmotic agents. Indeed, among the documents cited during the opposition and appeal procedures, three are concerned with dialysis fluids, namely documents (1), (3) and (10) and all of them are concerned with the use of an amino acid source material as osmotic agent. The Board thus considers that the various other possibilities offered by document (1) were no longer equally attractive for the skilled person, who was actually led by this trend to chose the "peptidic route".
  
10. The second question to be answered is whether the skilled man would have considered that reducing the size of the peptidic osmotic agent of document (1) would constitute an obvious solution to the problem.
  
11. In the Board's view the considerations of physics exposed above already (cf. point 8) lead to this solution, in so far as the skilled man would have deduced therefrom that, as far as the molecular weight of the osmotic agent is concerned, a compromise must be found between these two opposite requirements and that the ideal osmotic agent must have a molecular weight sufficiently high so as not to cross the peritoneal membrane and low enough to avoid solubility problems. It would have been a matter of routine "try-and-see" experiments to determine the suitable average length of the mixture of peptides.

12. Document (1) itself teaches towards such a modification by reference to the molecular weights of the different molecules used in the examples: their range extends from 5,000 to 40,000 and they all appear to be efficient under simulated dialysis conditions. It was argued that these molecules, being not only proteins (succinylated gelatin), but also sodium dextran sulfate and poly(ethylene maleate), cannot be compared in their function as an osmotic agent. This argument does not convince the Board. Indeed, as far as these molecules behave as osmotic agents and hence do not cross the membrane, their chemical nature is irrelevant. Only their molecular weights, which can influence their concentration in a dissolved state and hence their function as osmotic agent, are of importance. In so far, they can well be compared in their function as osmotic agents as demonstrated in Examples I-III of document (1) and in particular in Tables I-III.
  
13. Furthermore, document (1) uses both the terms "*polypeptides*" and "*proteins*" and therefore points to a distinction between these terms. This distinction can only be related for the skilled protein chemist to the molecular weight. Therefore, although only succinylated gelatin has been used as an example for a protein, document (1) also embraces shorter peptidic molecules.
  
14. In this context, the Board would like to consider an argument, which had originally been introduced by the respondent in view of the mixtures of peptides used for parenteral nutrition and referred to in documents (3) and (10), such as *Amigen* (documents (8), (13)). This argument is based on a teaching of document (13), according to which the peptides of *Amigen* (which are in average 3.5 amino acid residue long) are more poorly

retained by the kidneys than are the free amino acids. According to the respondent, this would have taught away from the use of such short peptides as an osmotic agent. The Board considers that this teaching does not contradict the consideration of physics mentioned above and would have been seen by the skilled man as an indication showing that the lowest limit of the peptide size must be higher than 3.5 amino acid residues in order to obtain a suitable osmotic agent.

15. Therefore, the second question is to be answered positively: the skilled man would have considered that the reduction of the size of the peptidic osmotic agent is a routine step towards the solution to the technical problem in view of document (1).
  
16. The third question is whether the skilled man would have used enzymic hydrolysis to obtain a mixture of peptides of a size suitable for CAPD.
  
17. The respondent answered this question negatively by citing document (1), column 5, lines 34 to 38, which states that the polypeptides and proteins can be **synthesized**, this term making reference to chemical synthesis. The Board acknowledges that chemical synthesis could be a possible way of preparing such a mixture of peptides on a bench scale level, but the Board is not convinced that chemical synthesis is the method of choice on an industrial scale level, because peptide synthesis is indeed a time-consuming, cumbersome, multi-step process unsuitable for a mass-production.
  
18. Another possibility would have been to use partial (alkaline or acid) chemical hydrolysis. Apart from the

fact that chemical hydrolysis *per se* is more adapted for complete hydrolysis leading to free amino acids, this possibility must also be considered as unsuitable, when seen in the context of CAPD. This form of dialysis aims at being far less restrictive for the patient than extracorporeal haemodialysis, in particular in avoiding to bind the patient several hours several times in a week to a dialysis machine. However, although CAPD is no longer performed under the close medical supervision of a skilled practitioner, the patient cannot be expected to carry out medical acts. Therefore, it is necessary that CAPD, and the ingredients therefor, be so prepared as to allow a standardized and easy dialysis procedure. This implies a rather high level of reproducibility and thus reliability, which has implications for the composition of the dialysis fluid. This requirement is not compatible with a partial chemical hydrolysis, since several parameters (such as temperature, duration of the hydrolysis, concentration of the acid or base and of the substrate) should then be tightly controlled in order to lead to a dialysis fluid of a constant composition.

19. Thus, enzymic hydrolysis would have been considered as the method of choice by the skilled man. The requirement of constant composition of the dialysis fluid implies the use of enzymes known to have a high specificity, such as trypsin or chymotrypsin, which will lead to a predictable and reproducible mixture of peptides after the so-called "complete hydrolysis" of a given protein, the conditions of which are easily determined by routine experiments. Moreover, enzymic hydrolysis was at the priority date of the patent in suit a well-known method not only used in food industry (documents (4), (6)), but also in medical nutrition



(documents (5), (6), (9), (11), (13)) and/or for immunological purposes (document (7)).

20. The fourth question is whether the skilled man would have obviously considered the use of casein for the preparation of the mixture of peptides.
21. It was well known at the priority date of the patent in suit (cf. document (2)) that casein falls within the scope of the definition of the protein and/or polypeptide given in document (1). Therefore, this question can already be answered positively.
22. However, the use of protein and/or polypeptides as an osmotic agent might only have been possible on a bench scale level, but not feasible on an industrial scale, because, for instance of the excessive costs of the peptide mixture. This was an argument presented by the respondent in view of document (3)(page 6, lines 6 to 13), that the Board would like to also take into consideration in view of document (1). The Board considers that this argument must be seen in its context, ie within the framework of document (3), within which it should be considered not in an absolute sense, but in a relative one. Indeed, it does not say that the cost of said amino acid source material is so prohibitive that its use *per se* as an osmotic agent cannot be taken into consideration, but it only states that, since glycerol is much cheaper and can also fulfil the function of an osmotic agent, the amino acid source material (in the context of document (3)) is only used as a nutrient. The Board's interpretation is corroborated by the wide use of amino acid source material (such as, but not only, sodium caseinate) in the prior art as demonstrated by documents (4)-(11),

(13)-(15).

23. The pH and the physiological salts mentioned in claim 1 cannot contribute to inventive step. CAPD, being performed *in vivo*, must respect the physiological requirements of the human body. This obviously implies that the pH of the dialysis fluid should be close to neutral and the composition such as allowing to dialyse away the toxins and waste products which are usually excreted by the kidneys without depleting the patient's blood in substances necessary for the fulfilment of the vital functions.
24. This view is supported by document (3) for instance, which mentions on page 4 (lines 24 to 27) that the dialysis is performed at a pH between 5.6 and 7.4 and on page 3 (lines 7 to 10) a preferred pH range of 5.6 to 7.2 is indicated. The pH value of 6.6 mentioned in claim 1 of the main request lies within these ranges and the respondent has not demonstrated that any particular importance for the performance of CAPD is related to this specific value.
21. In summary, the Board considers that the features mentioned above (point 7), considered alone or in combination, cannot confer an inventive step to claim 1 of the main request in view of the disclosure of document (1) considered together with well-known considerations of physics on dialysis.

## **Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairwoman:

U. Bultmann

U. Kinkeldey