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D E C I S I O N
of 27 January 1994

Case Number: T 0885/91 - 3.3.2

Application Number: 85900428.5

Publication Number: 0168425

IPC: A61K 31/23

Language of the proceedings: EN

Title of invention:
Parenteral nutrition with medium and long chain triglycerides

Applicant:
Clintec Nutrition Company, et al.

Opponent:
-

Headword:
Parenteral nutrition/CLINTEC

Relevant legal norms:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious use of suitable composition - no prejudice in the art"

Decisions cited:
G 0005/83, T 0019/86, T 0170/87

Catchword:
-

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Case Number: T 0885/91 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 27 January 1994

Appellant: Clintec Nutrition Company
Three Parkway North
Suite 500
Deerfield
Illinois 60015-0760 (US)

Representative: MacGregor, Gordon
Eric Potter & Clarkson
St. Mary's Court
St. Mary's Gate
Nottingham, NG1 1LE (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 26 June 1991 refusing European patent application No. 85 900 428.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P.A.M. Lançon
Members: L. Galligani
S.C. Perryman

Summary of Facts and Submissions

I. European patent application No. 85 900 428.5 filed and published as an International application under No. WO 85/03002 (European publication No. 0 168 425) was refused by the Examining Division.

The decision was taken on the basis of Claims 1 to 14 as filed by letter dated 21 January 1991.

Claim 1 read as follows:

" Use of LCTs in admixture with MCTs in the proportion of MCTs to LCTs ranging from 1:3 to 3:1 in the manufacture of a parenterally administrable nutritional solution for the purpose of ameliorating MCT toxicity in nutrition of a patient with liver disease."

Dependent Claims 2 to 14 related to specific embodiments of the use according to Claim 1.

The abbreviations LCT(s) and MCT(s) refer to triglyceride(s) of long chain fatty acids and triglyceride(s) of medium chain fatty acids, respectively.

II. The Examining Division refused the application under Article 97(1) EPC on the grounds that the subject-matter of the application did not involve an inventive step within the meaning of Article 56 EPC, having regard to the following documents:

(1) GB-A-2 084 172;

(2) The Am. J. Clin. Nutr., 1982, Vol. 36, No. 5, 950-962 (& Chem.Abstr., 1982, Vol.97, No. 214639s);

(3) EP-A-0 071 995.

The main reasons given for the decision are as follows:

(a) combinations of MCTs and LCTs for the nutrition of patients in a variety of illnesses, including - for instance - hepatitis, are known from the prior art (see documents (1) and (3)). In particular, document (3) shows that for emulsions of MCTs and LCTs with a weight ratio of 4:1 to 1:4 the bad tolerability of MCTs can be surmounted by admixing therein egg phosphatides;

(b) MCT/LCT mixtures are proposed in the present application as a solution to the problem of ameliorating, i.e. of decreasing, the toxicity of MCTs in nutrition of a patient with liver disease. The MCT/LCT emulsions according to the present application also contain egg phosphatides (see examples 1 and 2);

(c) it seems obvious for the skilled person to administer to patients having a liver disease or other diseases the known emulsions which have reduced side effects.

III. The Appellant lodged an appeal against this decision and paid the appeal fee. In support of its appeal the Appellant submitted two affidavits and the following additional documents:

(4) "Perspectives in Clinical Nutrition", J.M.Kinney & P.R.Borum Eds., URBAN & SCHWARZENBERG, Baltimore-Munich, 1989, pp. 393-403;

(5) Infusionstherapie, 1976, Vol. 3, pp. 129-132.

IV. In a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal, the Board invited the Appellant to oral proceedings and expressed some preliminary comments on the matter, relying in particular on reference (5).

V. In reply to the said communication the Appellant with letter dated 24 November 1993 withdrew its request for oral proceedings and requested a decision on the written submissions. It requested also amendment of Claim 1, namely the addition of the expression "but excluding liver abscess" at the end of the claim, and of the relevant description pages (pages 2 and 18) to exclude the case where the liver disease was a liver abscess.

VI. The Appellant's main arguments are essentially as follows:

(a) Although mixtures of LCTs and MCTs were known in the art as nutritional solutions, a clear prejudice existed against MCTs being fed parenterally to liver diseased patients, due to their toxicity (see documents 2 and 5). This prejudice was overcome by the present inventors who found that the toxicity of MCTs can be ameliorated by mixing therewith a proportion of LCTs. This finding is confirmed in the later document (4) which describes preclinical tests in which the ameliorating effect of LCTs on MCT toxicity is confirmed, although not specifically directed to liver diseased patients.

(b) Although document (3) discloses that egg phosphatide can improve the compatibility of the LCT/MCT mixtures, it does not disclose that the use of egg phosphatide in the emulsion would enable its intravenous feeding to liver diseased patients. On the other hand, the present application does not

always use egg phosphatide as an emulsifier. Example 2 and examples 5 and 6 which report the test results on mice and a clinical example, disclose the ameliorating effect of LCTs on MCTs with no egg phosphatide present.

(c) As for document (1), although it teaches lipid compositions including MCTs and LCTs for nutritional and therapeutic uses, it is concerned with disorders of the digestion of lipids or metabolic diseases. Hepatitis is mentioned merely in the list of diseases which cause a reduction in the bile salts. No consideration is given to the effects of MCTs and LCTs on the diseased liver. Thus, this document does neither disclose nor suggest the intravenous administration of a composition including MCTs to liver diseased patients.

(d) The authors of reference (5) were not aware of any contraindications for parenteral administration of MCTs to liver abscess patients. They were, however, aware of contraindications in the case of cirrhosis and other diseases. Contraindications for cirrhosis and other diseases in which the functional mass of the liver is reduced were still apparent in 1982 as shown by document (2). Thus, the disclaimer of liver abscess is sufficient for Claim 1 to be distinguished over the prior art in respect of Article 56 as well as Article 54 EPC.

VII. The Appellant requests that the appealed decision be set aside and that a patent be granted on the basis of the amended claims and description accompanying the letter of 24 November 1993.

Reasons for the Decision

1. The appeal is admissible.

2. *Formal allowability of the claims (Article 123(2) EPC)*

The amended claims which were considered in the decision under appeal are fairly based on the application as originally filed (see in particular page 6, second paragraph).

The exclusion of liver abscess from the scope of the Claim 1 now put forward as well as the deletion of the words "liver abscess" on page 2, penultimate line of the description does not result in the creation of subject-matter extending beyond the content of the application as filed.

The requirements of Article 123(2) EPC are, therefore, met.

3. *Novelty (Article 54 EPC)*

3.1 Claim 1 is in the form of a second medical use claim within the principles set out in Decision G 05/83, OJ EPO 1985, 64.

According to established EPO case law, such a formulation is acceptable if it relates either to a new and inventive therapeutic treatment or - for the same therapeutic application - to a particular novel group of patients having a medical condition for which this treatment had not previously been suggested (see Decision T 19/86 OJ EPO 1989, 24).

The therapeutic application identified in Claim 1 is a "sub-condition" of liver diseases, namely the condition in which MCT toxicity symptoms are produced upon parenteral nutrition of the patients with MCT-containing emulsions. In particular, according to the description, the said therapeutic application is directed to liver diseased patients which exhibit various degrees of compromised MCT metabolic capacity (see description, page 6 second paragraph).

3.2 Novelty was not contested by the Examining Division.

During the appeal proceedings, the Board raised in an official communication some doubts as regards novelty of the claimed matter *vis-à-vis* document (5). This document discloses the successful parenteral administration to a number of patients, *inter alia* to a patient with liver abscess, of a preparation of MCTs in admixture with LCTs (soya oil) in proportions falling within the range given in present Claim 1.

By introducing a disclaimer of liver abscess in Claim 1, the Appellant has now met the novelty objection based on document (5).

None of the other documents discloses the subject-matter of the present claims which is, therefore, novel.

4. *Inventive step (Article 56 EPC)*

The use of lipid emulsions in total parenteral nutrition was well known in the art. In particular, MCT emulsions and MCT/LCT emulsions were widely used as nutritional support in the treatment of a variety of disorders, in particular of disorders of lipid absorption (see

documents 1 to 5). Their enteral and parenteral administration also in disorders of the liver was known (see documents 1, 2 and 5).

4.1 (a) The closest prior art

In the Board's view, the closest prior art in the present case is represented by document (3) which addresses the problem of the bad tolerability of MCT-containing emulsions, in particular of MCT/LCT emulsions, during parenteral nutrition of patients (see page 2, second paragraph). This document shows that, if egg phosphatide is used as emulgator in LCT/MCT emulsions in place of the usual soya phosphatide or gelatine, the problem of the bad tolerability of MCTs is solved. In the emulsions disclosed in (3) the proportion of LCTs to MCTs ranges from 4:1 to 1:4. Trials are described to show the effects. No examples of the use of the said emulsions in specific diseases are provided.

Contrary to the statement of the Appellant (see Section VI, item (b), the emulsions exemplified in the present description seem always to contain egg phosphatides as emulgator, just like those disclosed in document (3). In fact, Examples 2 and 5 refer to the "MCT oil emulsion of Example 1" where egg phosphatides are used as emulgator. Example 6 (clinical test) generically refers to "MCT oil emulsion". However, in the context of the examples it must *prima facie* be assumed that the same emulsion as in the previous examples has been used, i.e. an emulsion with egg phosphatide as emulgator.

Both the present application and document (3) aim at ameliorating the MCT toxicity in parenterally administrable nutritional solutions.

The present application differs from document (3) essentially in that it specifically proposes the use of MCT/LCT emulsions for the parenteral nutrition of liver diseased patients, excluding patients with liver abscess.

The proportion of MCTs to LCTs in the emulsions according to the present application (from 1:3 to 3:1) falls wholly within the range given in document (3) (from 1:4 to 4:1), and includes the greater part of this range so that *prima facie* no distinction exists on the basis of any selection.

(b) The underlying technical problem

In the light of document (3) the technical problem underlying the present application can be seen in the manufacture of parenterally administrable MCT/LCT emulsions suitable for liver diseased patients.

(c) The solution proposed

As a solution to the said problem the Appellant proposes in Claim 1 the use of LCTs in admixture with MCTs in the proportion of MCTs to LCTs ranging from 1:3 to 3:1 in the manufacture of the emulsions. The claim itself is silent about the emulgator.

Since, as shown above (see item (a)), the MCT/LCT emulsions as exemplified in the present application are substantially the same as those of

document (3), the solution as formulated in Claim 1 amounts essentially to claiming the proposal of using the known emulsions in liver diseased patients. That the claims of the present application also cover some emulgator other than egg phosphatide does not assist the Appellant in distinguishing the nutritional solution of the present claims from that of document (3).

Example 6 in the present application reports an improvement in the patient's condition (alcoholic cirrhosis) after treatment with an MCT/LCT emulsion according to Claim 1. Accordingly, the Board is satisfied that the underlying technical problem has been solved.

(d) Assessment of inventive step

In the Board's view, when confronted with the question of manufacturing a parenterally administrable MCT/LCT emulsions specifically for liver diseased patients, the skilled person would have turned to those according to document (3) as being suitable therefor.

Document (3) draws attention to the side effects (haemolysis of red blood cells, narcotising effect, increase in free fatty acids and ketone bodies) linked to the administration of MCTs during parenteral nutrition of patients, no reference to a specific disease being made therein. This document proposes as a generally applicable solution to this problem the use of a combination of MCTs and LCTs (essentially in the same proportions as in the present case) with egg phosphatide. The trials

reported therein show that an improvement in the tolerability can thereby be obtained with elimination of side effects.

In the Appellant's view, one skilled in the art would not have been lead to use the known mixtures of LCTs and MCTs as intravenous nutritional solutions for liver diseased patients because a clear prejudice existed against MCTs being fed parenterally to such patients, due to their toxicity (see documents 2 and 5).

In the Board's opinion, the skilled person might possibly have had reservations with respect to their administration to patients suffering of liver cirrhosis because the intravenous use of MCTs was explicitly contraindicated for this liver disease (see documents 2 and 5), but certainly not with respect to their administration to other liver diseased patients. The reason therefor is that the skilled person would have considered the teaching of (3) as being the ready solution to the problem of the bad parenteral tolerability (toxicity) of MCT-containing lipid emulsions. In fact, document (3) had indicated how the side effects linked to the intravenous administration of MCTs could be overcome.

Contrary to the Appellant's submissions, the Board sees no evidence for any **general** prejudice against the use of MCT/LCT emulsions in liver diseases. In this respect it is observed that the successful parenteral administration to a **liver abscess** patient (undoubtedly, a liver diseased patient) of a preparation of MCTs in admixture with LCTs (soyaoil) in proportions falling within the range

given in present Claim 1 had been reported in document (5). Soya phosphatide was used therein as emulgator (see Tables I and II).

As already stated, an explicit contraindication existed only with respect to liver cirrhosis (see documents (2) and (5)). However, present Claim 1 is not restricted to liver cirrhosis, but is broadly directed to the manufacture of nutritional solutions for patients with liver diseases except liver abscess.

No prejudice has been shown to exist in respect of the use of egg phosphatide as emulgator in emulsions to be parenterally administered to liver diseased patients.

With respect to the emulgator, the Board observes also that the Appellant has not even shown that the observed technical effect (reduction of MCT toxicity) in the present case was not to be ascribed to the use of egg phosphatide as emulgator, as taught by document (3). In fact, as already stated above, the MCT/LCT emulsions exemplified in the two cases are substantially identical.

Therefore, in the Board's opinion, the skilled person had no reason to believe that an emulsion according to document (3) was not suitable for parenteral administration to a liver diseased patient.

The disclaiming of liver abscess is not sufficient to confer an inventive step to Claim 1. It is established practice that, although a disclaimer can be used to make an inventive teaching which

overlaps with the state of the art novel, it cannot make an obvious teaching inventive (see T 170/87, OJ EPO 1989, 441).

For the above reasons, the subject matter of Claim 1 lacks an inventive step.

4.2 None of the dependent claims contain any additional feature which, in combination with the features of the claims to which they refer, involve an inventive step. Said dependent claims relate to embodiments wherein ancillary features are specified which have not been shown to have a direct bearing on the technical effect and which seem to be within the normal design freedom of the skilled person.

Order

For these reasons, it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

P.Martorana P.A.M.Lançon