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Case Number: T 0392/14 - 3.3.09

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Language of the proceedings: EN

Title of invention:

COMPOSITIONS AND METHODS FOR IMPROVING FUNCTIONAL VASCULAR INTEGRITY, CELLULAR SURVIVAL AND REDUCING APOPTOSIS AFTER AN ISCHEMIC EPISODE IN THE BRAIN

Patent Proprietor:

Nestec S.A.

Opponents:

Fresenius Kabi Deutschland GmbH
N.V. Nutricia

Headword:

Relevant legal provisions:

EPC Art. 56

Keyword:
Inventive step - reasonable expectation of success (yes)

Decisions cited:

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0392/14 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 15 April 2016

Appellant: (Patent Proprietor)	Nestec S.A. Avenue Nestlé 55 1800 Vevey (CH)
Representative:	Kingsbury, Oliver William Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 1)	Fresenius Kabi Deutschland GmbH Else-Kröner-Str. 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Else-Kröner-Straße 1 61352 Bad Homburg (DE)
Respondent: (Opponent 2)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 December 2013 revoking European patent No. 1919304 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	W. Sieber
Members:	M. O. Müller
	E. Kossonakou

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the proprietor of European patent No. 1 919 304 against the decision of the opposition division to revoke it.

II. With their oppositions, opponents 1 and 2 had requested revocation of the patent in its entirety on the grounds of Article 100(a) (lack of novelty and inventive step), 100(b) and 100(c) EPC.

III. The documents submitted during the opposition proceedings included:

O3: M. Okada et al., Neuroscience, volume 71(1), 1996, pages 17 to 25;

O5: EP 0 810 829 B1;

O6: WO 96/36327 A1;

O7: US 5,385,940 A;

O10: U.N. Das, Nutrition, volume 17, 2001, pages 337 to 346;

O12: U.N. Das, Nutrition, volume 19, 2003, pages 686 to 692;

O13: K. Nobuaki et al., Japanese Journal of Surgical Metabolism and Nutrition, volume 38(5), 2004, abstract;

O14: A.A. Brown et al., Am. J. Clin. Nutr., volume 73, 2001, pages 673 to 686; and

O18: WO 95/16661 A1.

IV. The opposition division's decision was based on a main request and auxiliary requests 1 to 3.

The main request was rejected since the inclusion of a new dependent claim, namely claim 2, did not meet the requirements of Rule 80 EPC.

The independent claims of auxiliary request 1 read as follows:

> "1. Use of one or more long chain polyunsaturated fatty acid (LCPUFA) and one or more nitric oxide releasing compound (NORC) in the manufacture of a medicament or medicaments for co-administration for reducing ischemia-induced brain injury in an animal."
>
> "2. A composition comprising one or more LCPUFA and one or more NORC for use in reducing ischemia-induced brain injury in an animal, wherein the composition is administered to the animal on a regular basis."
>
> "10. A composition comprising one or more LCPUFA and one or more NORC for use in reducing ischemia-induced brain injury in an animal."

Auxiliary request 1 was considered to be novel. The subject-matter of claim 1 was however not regarded as inventive. The subject-matter of this claim differed from the closest prior art O7 by the additional use of LCPUFAs. Even if the problem was considered to be the further reduction of ischemia-induced brain injury, the claimed solution was obvious in view of O7 in

combination with O3. The latter document was in the same technical field as O7 and disclosed that ischemia-induced brain injury could be reduced by the administration of LCPUFAs.

The subject-matter of claim 1 of auxiliary request 2 differed from claim 1 of auxiliary request 1 only in that it required the medicament to be administered on a regular basis. This feature did not change the conclusion as given with regard to auxiliary request 1, because such a mode of administration was common medical practice.

The subject-matter of claim 1 of auxiliary request 3 differed from claim 1 of auxiliary request 2 in that it further defined the LCPUFA to be an (n-3) LCPUFA and the NORC to be L-arginine or derivatives thereof. Since O7 disclosed the use of L-arginine and O3 the use of an (n-3) LCPUFA, this amendment did not change the conclusion as given with regard to auxiliary request 1.

V. The proprietor (hereinafter: the appellant) filed an appeal and with its statement setting out the grounds of appeal submitted a main request and auxiliary requests 1 and 2 as well as:

O22: F. Zhang et al., Stroke, volume 27(2), 1996, pages 317 to 323.

VI. Responses were filed by opponents 1 and 2 (hereinafter: respondents 1 and 2), with respondent 2 requesting that O22 not be admitted into the proceedings.

VII. With its communication dated 11 November 2015, the board issued its preliminary opinion in which it *inter alia* commented on inventive step in view of O3 and O7.

VIII. With its letter dated 1 March 2016, the appellant filed a new main request and new auxiliary request 1 to replace all previous requests.

The independent claims (claims 1 and 8) of the main request read as follows:

> "1. Use of one or more long chain polyunsaturated fatty acid (LCPUFA) and one or more nitric oxide releasing compound (NORC) in the manufacture of a medicament or medicaments for co-administration for reducing ischemia-induced brain injury in an animal, wherein the medicament is administered to the animal on a regular basis and wherein the LCPUFA is one or more of an (n-3) LCPUFA and the NORC is one or more of L-arginine and derivatives thereof."

> "8. A composition comprising one or more LCPUFA and one or more NORC for use in reducing ischemia-induced brain injury in an animal, wherein the composition is administered to the animal on a regular basis and wherein the LCPUFA is one or more of an (n-3) LCPUFA and the NORC is one or more of L-arginine and derivatives thereof."

The independent claims (claims 1 and 8) of auxiliary request 1 read as follows (amendments with regard to the main request in bold type):

> "1. Use of one or more long chain polyunsaturated fatty acid (LCPUFA) and one or more nitric oxide releasing compound (NORC) **in an amount effective to reduce ischemia-induced brain injury in the event of an ischemic episode in the brain of an animal** in

the manufacture of a medicament or medicaments for co-administration for reducing ischemia-induced brain injury in an animal, wherein the medicament is administered to the animal on a regular basis and wherein the LCPUFA is one or more of an (n-3) LCPUFA and the NORC is one or more of L-arginine and derivatives thereof."

"8. A composition comprising one or more LCPUFA and one or more NORC **in an amount effective to reduce ischemia-induced brain injury in the event of an ischemic episode in the brain of an animal** for use in reducing ischemia-induced brain injury in an animal, wherein the composition is administered to the animal on a regular basis and wherein the LCPUFA is one or more of an (n-3) LCPUFA and the NORC is one or more of L-arginine and derivatives thereof."

IX. With its letter dated 13 April 2016, respondent 2 filed:

O23: "Myocardial Ischemia and Preconditioning", N.S. Dhalla et al. (ed.), Springer Science + Business Media, New York 2003, page 468.

X. At the oral proceedings held on 15 April 2016, respondent 2 withdrew its request that O22 not be admitted and the appellant requested that O23 not be admitted into the proceedings.

XI. So far as relevant to the present decision, the appellant's arguments can be summarised as follows:

The claimed subject-matter was inventive. The subject-matter of claims 1 and 8 differed from the closest

prior art O3 in that L-arginine was additionally present as active ingredient. The problem solved in view of this document was the provision of a medicament that further reduced ischemia-induced brain injury. Contrary to the respondents' assertion, the skilled person could not be certain that this problem would be solved by adding the L-arginine of O7 to the DHA of O3. It was by no means a generally accepted principle in the field of medicine that the pharmacological effects of two different compounds administered in combination were cumulative. In fact O6 and O22 proved that a prejudice existed in the art against combining (n-3) LCPUFAs with L-arginine to reduce ischemia-induced brain injury.

O23 should not be admitted into the proceedings since it had been filed too late to be able to get an expert opinion about it.

XII. So far as relevant to the present decision, the respondents' arguments can be summarised as follows:

The subject-matter of claims 1 and 8 was not inventive, taking as the closest prior art (i) O7 (in combination with O3), (ii) O3 (in combination with O7) or (iii) O6 (in combination with O3 and O7). As regards approach (ii), the claimed subject-matter differed from O3 in that L-arginine was additionally present. The problem solved in view of this document was how to provide an improved way of reducing ischemia-induced brain injury. The solution as claimed was obvious in view of O7 which taught the use of L-arginine to reduce the infarct volume after brain ischemia. Contrary to the appellant's assertion, there was no general prejudice in the art against combining two components having the same therapeutic effect and no such

prejudice could be derived from O6, which actually taught the skilled person to apply a combination of (n-3) LCPUFAs and L-arginine. Such a prejudice against using the L-arginine of O7 could not be derived from O22 either. The teaching of this document would not be regarded as relevant by the skilled person since, unlike in O7, L-arginine was applied therein only after brain ischemia had occurred.

These inventive-step arguments also applied to auxiliary request 1.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or auxiliary request 1, both filed with letter dated 1 March 2016.

The appellant additionally requested that O23 not be admitted into the proceedings.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

Main request

1. Inventive step

1.1 The invention concerns a composition suitable for protection against cellular damage associated with an ischemic episode in the brain. The composition is in particular suitable for reducing damage caused by brain ischemia (paragraph [0001]).

1.2 O3 describes a study that investigates whether chronic administration of the (n-3) LCPUFA docosahexaenoic acid (hereinafter DHA) is able to provide protection against hippocampal neuronal damage induced by cerebral ischemia in rats (abstract). It is thus in the same technical field and has the same objective as the opposed patent. In line with the arguments of all parties, O3 can thus be considered to represent the closest prior art.

Various doses of DHA were administered to the rats daily over 21 days (abstract and "Drug treatment" on page 18). After the 21-day administration, transient forebrain ischemia was induced in the rats by occlusion of the cerebral blood supply for 10 minutes (abstract and "Surgical procedure" on page 18). Thereafter they were subjected to a behavioural test for eight days, killed and the neuronal densities in the hippocampus CA1 sub-field were determined ("Neuropathological analysis" on page 18). It was found that the chronic administration of DHA significantly reduced the neuronal damage to the hippocampus caused by the induced transient forebrain ischaemia (abstract and second paragraph in the left-hand column of page 23).

Both parties agreed that the subject-matter of independent claims 1 and 8 differs from O3 in that the composition used for the therapeutic treatment contained L-arginine in addition to DHA.

1.3 The appellant argued that the problem solved over O3 was the provision of a medicament that further reduced ischemia-induced brain injury.

1.4 As a solution to this problem, the patent proposes the use and composition of claims 1 and 8, characterised by

the feature that L-arginine is present in addition to (n-3) LCPUFAs.

1.5 It needs to be examined whether the problem referred to by the appellant has been credibly solved by this feature.

1.5.1 In the example of the patent (denoted "Example 1"), rats were fed a specific diet ad libitum over four weeks. In one group (group 4), the diet was supplemented with 2 wt% menhaden fish oil and 2 wt% arginine (diet II). In another group (group 5), the diet was supplemented with 2 wt% menhaden fish oil only (diet III). After the four-week feeding period, both groups of rats were subjected to transient middle cerebral artery (tMCA) occlusion to induce brain ischemia. After 60 minutes, the occlusion was removed to allow reperfusion of the brain. At 24 hours after the onset of reperfusion, the animals were killed and the stroke volume and extent of apoptosis were assessed.

As not disputed by the parties, diet II of the example of the patent, which contains menhaden fish oil - and thus (n-3) LCPUFAs - and arginine, corresponds to a composition according to claims 1 and 8. Diet III, which contains the menhaden fish oil, and thus (n-3) LCPUFAs only, corresponds to the teaching of O3. As can be seen in figures 1 to 3 of the patent, the ischemic lesion and the percentage of apoptotic cells obtained with the diet according to claims 1 and 8 (diet II) was lower than with the diet supplemented with menhaden fish oil only (diet III).

It is thus credible that the problem of providing a medicament that further reduces ischemia-induced brain

injury is solved over O3, at least if, as is the case in the example of the patent, the (n-3) LCPUFA and arginine are administered before brain ischemia occurs.

1.5.2 Claims 1 and 8 however cover two alternatives, (a) and (b), one relating to regular administration prior to the occurrence of brain ischemia and the second one to administration only after brain ischemia has occurred. The respondent argued that for the latter alternative, the claimed therapeutic effect of reducing ischemia-induced brain injury could not be plausibly obtained, and that the problem referred to by the appellant had thus not been credibly solved over the entire scope of claims 1 and 8. Even though the board has some sympathy for this argument, it will hereinafter assume in the appellant's favour that the problem referred to by the appellant is solved also for alternative (b), i.e. if the (n-3) LCPUFA and L-arginine are administered after brain ischemia has occurred and thus that this problem forms the objective technical problem.

1.6 It needs to be examined whether under this assumption the claimed solution, i.e. the use of L-arginine in addition to DHA, is obvious.

1.6.1 The skilled person searching for a method of reducing ischemia-induced brain injury even further would look into O7, since this document relates to this very problem, namely the treatment of stroke, i.e. the death of brain tissue following an interruption of cerebral blood supply (column 1, lines 13 to 15).

1.6.2 O7 discloses a study in which ischemia-induced brain injury was provoked in rats by temporary blockage (MCA occlusion) of the brain's blood supply. At 16 and 3 hours before and 5 and 120 minutes after the

temporary blockage, three groups of rats were administered a control diet without arginine, a diet containing L-arginine and a diet containing D-arginine, respectively. Compared to the control diet and that containing D-arginine, the L-arginine diet reduced the infarct volume and area (column 3, first and second full paragraphs and column 6, line 56 to column 7, line 18). The reduction of the infarct volume and area corresponds to the claimed therapeutic effect of reducing ischemia-induced brain injury.

1.6.3 In view of this teaching, the skilled person would, with a reasonable expectation of success, have tried to further reduce ischemia-induced brain injury by adding the L-arginine of O7 to the DHA diet of O3. He would thereby have arrived at alternative (a) of claims 1 and 8. The subject-matter of this alternative is thus obvious over O3 in combination with O7, even if one considers the problem defined by the appellant to be the objective technical problem.

1.6.4 The appellant argued that the skilled person starting from O3 and using DHA could not be certain that the problem of further reducing ischemia-induced brain injury would be solved by adding the L-arginine of O7. It was by no means a generally accepted principle in the field of medicine that the pharmacological effects of two different compounds administered in combination were cumulative. Each of the compounds could already be capable of eliciting the maximum possible biological response, so that the addition of the second compound would not further improve the response. It could equally be possible that one compound in fact counteracted the other, thereby negating its effect and resulting in a reduced response for the combination compared with the individual components.

The board is not convinced by these arguments.

Firstly, an invention is obvious not only if there is certainty that, when modifying the teaching of the prior art such as to arrive at the claimed subject-matter, the objective technical problem is solved. The existence of a reasonable expectation of success is actually sufficient for a claimed invention to be obvious.

Secondly, it is quite common in the medical field for two or more active ingredients with the same therapeutic effect to be co-administered in order to enhance that effect. For instance, as set out by respondent 1, ACE inhibitors and beta blockers are combined to treat hypertension, Clopidogrel® and acetylsalicylic acid to prevent thrombosis, Zivovudin® and Abacavir® to treat HIV, Interferon and Ribavirin® to treat hepatitis C, and Amoxycillin and Clarithromycin to treat an infection with Helicobacter Pylori. The skilled person would thus have a reasonable expectation of success that the combination of two components with the same therapeutic effect would enhance that effect.

1.6.5 The appellant furthermore argued that O6 proved that a prejudice existed in the art against combining (n-3) LCPUFAs with L-arginine to reduce ischemia-induced brain injury. More specifically, example 1 of O6 showed that a combination of fish oil, and hence (n-3) LCPUFAs, and arginine were - in terms of the lactate dehydrogenase (LDH) level - no better and - in terms of the malondialdehyde (MDA) level - even worse than arginine alone. Accordingly, in view of O6 the

skilled person would not combine the (n-3) LCPUFA of O3 with the L-arginine of O7.

In example 1 of O6, three groups of rats were fed, ad libitum for 12 to 19 days, diets containing (i) corn oil (which does not contain any (n-3) LCPUFA or L-arginine), (ii) encapsulated fish oil (which contains (n-3) LCPUFAs), and (iii) encapsulated fish oil and L-arginine. Thereafter, the livers of the rats were removed and perfused at low flow rates for 75 minutes to render them anoxic. Subsequently, the livers were reperfused at normal flow rates. LDH and MDA levels and the distribution time in a trypan blue infusion test were assessed.

The board acknowledges that in terms of the MDA levels thus determined, fish oil and arginine combined are worse than arginine alone. More specifically, the amount of MDA (a biomarker used to measure the level of oxidative stress in an organism) was higher for the group of rats fed the combination of fish oil and arginine (67 nmol/g/h) than for the group fed with arginine alone (45 nmol/g/h), even though fish oil alone (80 nmol/g/h) and arginine alone (45 nmol/g/h) were better than the control (90 nmol/g/h). However, when discussing MDA results, O6 (first full paragraph of page 9) states that the differences between the various groups were not statistically significant. The skilled person reading O6 would thus have been very cautious about this result.

In fact, looking at the two other characteristics, the LDH level (an index of cellular or tissue damage) and the trypan blue distribution time (an index of the extent of blood microcirculation in the liver), the

skilled person would be taught by O6 to use the fish oil and L-arginine in combination:

O6 indeed concludes the discussion of the LDH results (paragraph bridging pages 8 and 9) with the statement that "Taken together, reperfusion injury, which occurs when oxygen is re-introduced into previously anoxic liver, is minimized by pre-feeding rats a diet supplemented with fish-oil and arginine".

As regards the trypan blue distribution time, O6 (second full paragraph on page 9) states that hepatic microcirculation is restored the fastest if the rats are pre-fed with encapsulated fish-oils supplemented with L-arginine. O6 emphasises that "These results are extremely significant ($p<0.05$, Student's T Test)". In this respect, the appellant's argument that the trypan blue test was not indicative of cell damage or death and hence of the organ's injury is not convincing, since it is contradicted by O5. More specifically, in the same way as O6, O5 is concerned with reperfusion injury in a low flow - reflow liver perfusion model (page 9, line 7) and states that the trypan blue test is used to assess microcirculation and cell death (page 9, line 25) and that trypan blue uptake indicates irreversible loss of cell viability (page 9, line 45).

In agreement with the LDH and trypan blue test results, O6 refers to the use of a combination of L-arginine with (n-3) LCPUFAs as a preferred embodiment (first paragraph on page 5).

Hence, contrary to the appellant's assertion, O6 does not provide any prejudice against but in fact teaches the use of LCPUFAs in combination with L-arginine.

Hence, alternative (a) of claims 1 and 8 is still not inventive.

1.6.6 The appellant argued furthermore that according to O22, L-arginine worsened ischemic damage. Hence, also in view of this document, the skilled person would not assume that the combination of DHA as disclosed in O3 with the L-arginine as disclosed in O7 would lead to a further reduction of ischemia-induced brain injury.

O22 describes a study in which rats were subjected to MCA occlusion to induce brain ischemia. 24 hours after this intervention, one group of rats received L-arginine alone for three consecutive days. On the fourth day, the rats were killed and the infarct volume was determined (abstract and "Effect of AG and/or Arginine on Infarct Volume and Water Content" on page 318). It was indeed found that the infarct volume was increased and thus ischemic damage was worsened by the administration of L-arginine alone (abstract and "Effect of AG or L-arginine on Infarct Water Content" on page 320).

However, unlike in O7, the L-arginine is administered in O22 for the first time 24 hours after brain ischemia had occurred. Hence, the skilled person would not necessarily transfer the result obtained in O22 to O7, where L-arginine treatment already starts 16 hours before the ischemic event, in particular in view of the finding in O7 that this significantly decreases the infarct size (conclusion on figure 4 in the first and second full paragraph of column 3).

1.6.7 The above finding that the subject-matter of claims 1 and 8 is obvious from the combination of O3 with O7 thus remains valid. The subject-matter of claims 1 and

8 thus lacks inventive step in view of this combination of documents. The main request is therefore not allowable.

1.7 Admission of O23

The appellant requested that O23, which was filed by respondent 2 with its letter dated 13 April 2016, not be admitted into the proceedings.

Respondent 2 filed O23 to show that it was controversial at the priority date of the patent whether the MDA level as referred to in O6 was a relevant indicator to assess cell damage.

The appellant had already in its statement of grounds of appeal relied on the MDA test results in O6. Respondent 2 thus could and should have provided O23 already in its response to the statement of grounds of appeal. By not submitting it until shortly before the oral proceedings, the respondent prevented the appellant from being able to get an expert opinion about it. The board therefore decided not to admit O23 into the proceedings.

Auxiliary request 1

2. Inventive step

2.1 Independent claims 1 and 8 of auxiliary request 1 differ from claims 1 and 8 of the main request by the addition of the wording "in an amount effective to reduce ischemia-induced brain injury in the event of an ischemic episode in the brain of an animal".

This amendment was made to address an objection raised by respondent 2 under Article 123(2) EPC and, as not disputed by the appellant during the oral proceedings, does not change anything with regard to the assessment of inventive step. Therefore, for the same reasons as given above for the main request, the subject-matter of claims 1 and 8 of auxiliary request 1 lacks inventive step in view of O3 in combination with O7. Auxiliary request 1 is thus not allowable.

3. In view of the above, the board did not decide on the respondents' further objections, namely lack of inventive step taking O6 or O7 as the closest prior art, insufficiency of disclosure and non-compliance with Articles 123(2), 84 and 54 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Cañueto Carbajo W. Sieber

Decision electronically authenticated