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Datasheet for the decision of 20 August 2019

Case Number: T 0012/15 - 3.3.01

Application Number: 02780164.6

Publication Number: 1443920

IPC: A61K31/202, A61K31/4415, A61K31/519, A61K31/714, A61P25/00

Language of the proceedings: EN

Title of invention:
PREPARATION FOR IMPROVING THE ACTION OF RECEPTORS

Patent Proprietor:
N.V. Nutricia

Opponents:
Fresenius Kabi Deutschland GmbH
Société des Produits Nestlé S.A.

Headword:
Compositions comprising PUFAs, B Vitamins and uridine or cytidine to be used in neurological disorders/NUTRICIA

Relevant legal provisions:
EPC Art. 83, 56
RPBA Art. 12(4), 13

Keyword:

Sufficiency of disclosure - (yes)
Inventive step - improvement not credible - obvious alternative
Late-filed evidence - submitted with the statement of grounds of appeal - admitted (yes)
Late-filed request - submitted during oral proceedings - admitted (yes)

Decisions cited:

T 1311/15, T 2001/12, T 1599/06, T 0609/02

Catchword:

Europäisches Patentamt
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Office européen des brevets

Beschwerdekammern

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Case Number: T 0012/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 20 August 2019

Appellant: (Patent Proprietor)	N.V. Nutricia Postbus 1 2700 MA Zoetermeer (NL)
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Representative:	Rupp, Christian Mitscherlich PartmbB Patent- und Rechtsanwälte Sonnenstraße 33 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 November 2014 revoking European patent No. 1443920 pursuant to Article 101(2) and Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	G. Seufert
	M. Blasi

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking the European patent no. 1 443 920.

II. The claims as granted consist of 26 claims, with claim 1 reading as follows:

A preparation for use in the treatment of a disorder selected from Parkinson's disease, Huntington's chorea, epilepsy, schizophrenia, paranoia, depression, sleep disorders, impaired memory function, psychoses, dementia and ADHD, said preparation comprising:

i) polyunsaturated fatty acids comprising at least docosahexaenoic acid;
ii) one or more components which have a beneficial effect on total methionine metabolism selected from the group consisting of vitamin B12, vitamin B6, folic acid, zinc and magnesium;
iii) at least 50 mg nucleobases, including uridine or cytidine, or the phosphates thereof, per daily dose.

Independent claims 14 and 25 are directed to a preparation containing the components i), ii) and iii) in a daily dose unit and to the use of components as defined in claim 1 in the preparation of a medicament for the treatment of disorders as defined in claim 1.

III. The present decision refers to the following documents:

D3 DE 36 88 769
D4 DE 38 75 286
D5 WO 98/48788

D9a Translation of WO 94/05319 from Japanese into German

D21 WO 00/06174

D22 WO 94/28913

D26 WO 01/03696

D29 WO 01/84961

D31 A. Fugh-Berman, J. M. Cott, Psychosomatic Medicine, 1999, 61, pages 712 to 728

D33 P. J. Rogers, Proceedings of the Nutrition Society 2001, 60, pages 135 to 143

D47 Experimental data, filed during the examination procedure and re-submitted during the opposition proceedings with letter 5 August 2013, three pages

D48 Experimental data, filed during the examination procedure and re-submitted during the opposition proceedings with letter 5 August 2013, four pages

D52 J. Jakubík, E. E. El-Fakahany, Pharmaceuticals 2010, 3, pages 2838 to 2860

D53 P. J. M. Savelkoul *et al.*, Journal of Neurochemistry, 2012, 120, pages 631 to 640

D54 "Anatomie Physiologie Pathophysiologie des Menschen", G. Thews *et al.*, 5th edition, 1999, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart(DE), pages 656, 657, 681 to 683, 695, 696

D55 "Mutschler Arzneimittelwirkungen", E. Mutschler *et al.*, 8th edition, 2001, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart(DE), pages 158, 160, 161, 171, 172, 197 to 200, 299 to 313

D56 J. L. Berkeley, A. I. Levey, Journal of Neurochemistry, 2000, 75, pages 487 to 493

D58 D. Riemann *et al.*, J. Psychiat. Res., 1994, vol. 28, no. 3, pages 195 to 210

The board notes that the parties started the numbering of the documents filed during the appeal proceedings with D52. A different document with that number had already been filed during the opposition proceedings (see decision under appeal page 2, point 1.9). Since the latter was not relevant during the appeal proceedings and in order to avoid confusion, the board adopted the numbering provided by the parties.

IV. Notices of opposition were filed by opponents 1 and 2 (respondents 1 and 2) requesting revocation of the patent in its entirety on the grounds of lack of novelty, lack of inventive step, insufficiency of disclosure and added subject-matter (Article 100(a), (b) and (c) EPC).

V. The decision under appeal was based on the patent as granted (main request) and the set of claims according to the first auxiliary request filed on 9 October 2014 at the oral proceedings before the opposition division.

The opposition division decided that the patent as granted did not contain subject-matter which extended beyond the content of the application as filed and that the invention of the patent in suit was sufficiently disclosed. The subject-matter of claim 14 as granted was considered to be anticipated by the prior art. The claims of auxiliary request 1 were held to comply with Articles 123(2) and 84 EPC. The subject-matter of claim 1 was considered novel, but not inventive in view of the combination of documents D26 and D21. In its assessment of inventive step, the opposition division considered that the improvement shown in documents D47 and D48 could not be extrapolated to receptors other than the muscarinic M1 receptor. Consequently, it formulated the problem to be solved as the provision of

an alternative composition for treating the claimed disorders.

VI. With the statement of grounds of appeal the appellant defended the patent as granted and submitted claims of auxiliary requests 1 and 2. It also filed documents D52 and D53.

VII. In their replies to the statement of grounds of appeal, the respondents maintained their objections of added subject-matter, insufficiency of disclosure and lack of novelty and inventive step, and raised objections against the admission of documents D52 and D53 and auxiliary requests 1 and 2 into the appeal proceedings. Additional documents, including documents D54, D55, D56 and D58, were filed.

VIII. With letter of 19 June 2019, the appellant filed "corrected" versions of auxiliary requests 1 and 2.

IX. With letters of 18 July 2019 and 2 August 2019 the respondents provided further arguments in support of their case. They also objected to the admission into the appeal proceedings of auxiliary requests 1 and 2, filed with letter of 19 June 2019.

X. At the oral proceedings before the board, the appellant filed a set of claims according to auxiliary request 1, on which the decision under appeal was based, and withdrew the previous auxiliary requests 1 and 2 filed with the statement of grounds of appeal and the "corrected" versions of auxiliary requests 1 and 2 filed on 19 June 2019.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that the feature "**said one or more**

components containing a combination of (a) vitamin B12; vitamin B6; and (c) folic acid;" has been added to component ii). Claim 14 as granted and its dependent claims 15 to 24 have been deleted and the remaining claims renumbered. The same feature as in claim 1 has been added to claim 13, which corresponds to claim 25 as granted.

XI. The appellant's arguments, as far as they concern the decisive issues of the present decision, can be summarised as follows:

- Admission of documents D52 and D53

These documents should be admitted into the proceedings. They were filed as a direct response to arguments which had been raised for the first time at the oral proceedings before the opposition division. The appellant had been unaware that the missing link between the muscarinic M1 receptor and the claimed diseases was an issue, as it had not been addressed during the written stage of the opposition proceedings. Nor had it been argued previously that the effect observed in D47 and D48 could not be attributed to the specific muscarinic M1 receptor. D52 confirmed the involvement of muscarinic M1 receptors in the claimed disorders. D53 confirmed that the effect observed in D47 and D48 was linked to the muscarinic M1 receptor.

- Sufficiency of disclosure

The application provided a plausible technical concept. The invention related to the improvement of receptor action, in particular the improvement of receptor sensitivity to neurotransmitters (see page 1, lines 4 to 5). Information as to receptor functioning, the role

of neurotransmitters and their involvement in disorders, such as neurological disorders, were explained in the application (see page 1, line 7 to page 3, lines 12, in particular page 2, line 31 to page 3, line 1). In the paragraph bridging pages 9 and 10, it was disclosed that the preparations according to the invention were used to improve the action of receptors in cells of the central nervous system. This disclosure was followed by the list of specific disorders, the severity of which could be reduced by increasing receptor action (see page 10, lines 12 to 17). The application also contained an example which demonstrated an effect on three different receptor types, including the muscarinic M1 receptor (page 11, line 18). Results were provided in Table 2 on page 12. Furthermore, it was explained on page 11, lines 29 to 32 that membrane fluidity facilitated conformational changes and in turn the activation of receptors, such as the muscarinic M1 receptor. The example demonstrated the effect of components i) and ii). It was, however, plausible that due to its involvement in neurotransmitter synthesis (see page 8, line 3 to 4 and page 9, line 19), component iii) worked together with components i) and ii) in disorders associated with neurotransmitter malfunctioning.

Furthermore, it was common general knowledge that M1 receptors, which were exclusively present in neuronal structures, were linked to cognitive processes and functions (see D52, D54 and D56). It was also common general knowledge that cognitive impairment was a symptom in dementia, Parkinson's disease, depression, schizophrenia, epilepsy or Huntington's disease, and even sleep disorders (see for example D54, D55 and D58). The muscarinic M1 receptor and the claimed disorders were therefore linked. Documents D47 and D48

supported the plausible technical concept disclosed in the application. Document D53 confirmed that the model used in D47 and D48 was correct and that the effect observed in D47 and D48 was due to activation of the muscarinic M1 receptor (see page 637, right-hand column, lines 20 to 28 in combination with page 633, left-hand column, lines 12 to 15). D47 and D48 also showed that an effect could be achieved with very low amounts of uridine.

- Inventive step

Document D26 was a suitable starting point for the assessment of inventive step. The distinguishing feature was the inclusion of an additional component, namely a source of nucleobases including uridine or cytidine, as outlined in the decision under appeal. The technical effect was a significant, i.e. synergistic, improvement in receptor activation. The effect had been demonstrated by D47 and D48. From Figure 1 of D48 it was apparent that a mixture of components i), ii) and iii) was better than the control (see comparison of conditions A and D). It was also apparent that a mixture of components i), ii) and iii) further improved receptor activation compared with a mixture of components i), ii) and phospholipids. Phospholipids were known to activate receptors (see D29). Uridine on the contrary was shown to be ineffective (see condition C). It could therefore be deduced that uridine improved receptor activation, even in the absence of direct comparison with the prior art. The same applied with regard to Figure 1 of D47. Since cytidine was converted into uridine (see D21), the same improvement was expected when cytidine was used. The use of mixtures of nucleotides in condition C compared with the use of a single nucleotide in condition A was

not significant. In D48 the total amount of nucleotides was the same as in condition A, and in D47 the amount of uridine was practically the same (i.e. 9 µg uridine monophosphate (and 25 µg cytidine monophosphate)) as in condition A (10 µg uridine monophosphate); both times no effects were observed.

Document D26 was silent on neurotransmitters. Thus starting from D26, the skilled person would not have expected the combination of components i) and ii) with a source of nucleobase to improve receptor function and therefore receptor-linked disorders. D26 did not mention nucleobases. There was no incentive in D21 either, which was silent as to neurotransmitter receptor functioning and had a different aim from D26, which dealt with homocysteine metabolism and homocysteine-lowering components. Even if the skilled person had considered document D21, since it dealt with disorders which overlapped with D26, he would have had no reason to believe that D21 could help promote cysteine-lowering components. There was no reasonable expectation of success that uridine could further aid homocysteine metabolism. Moreover, D26 strongly discouraged combining components i) and ii) with further components (see page 8, lines 8 to 13) and explained that care should be taken when using the essential fatty acids in nutrition. Furthermore, the observed synergistic effect was unexpected and surprising, even if the skilled person had considered combining the disclosure of document D26 and D21.

- Admission of auxiliary request 1

Auxiliary request 1 was the exact same request as auxiliary request 1 on which the decision under appeal was based. It had always been the intention to maintain

this request, as could be seen from the statement of grounds of appeal (page 3, fourth complete paragraph). It had, however, been realised that even the corrected version filed on 19 June 2019 was not identical in all respects to auxiliary request 1 on which the decision under appeal was based.

- Inventive step

Claim 1 of auxiliary request 1 differed from claim 1 as granted in that component ii) contained a combination of three compounds. This combination better reflected the composition that was used in the experimental evidence which supported an inventive step.

XII. The respondents' arguments, as far as they concern the decisive issues of the present decision, can be summarised as follows:

- Admission of documents D52 and D53

These documents should not be admitted into the appeal proceedings. They were late-filed and *prima facie* not relevant. D52 did not demonstrate the involvement of the muscarinic M1 receptor in the treatment of all claimed disorders, but merely confirmed its undisputed role in cognitive functions. Document D53 was known to the appellant before the opposition proceedings started. It could and should have been filed during the opposition proceedings in view of the objections regarding sufficiency of disclosure and inventive step. No new issues were raised at the oral proceedings before the opposition division.

- Sufficiency of disclosure

The claimed invention was not sufficiently disclosed because the application failed to provide suitable evidence that the claimed therapeutic effect – in the present case the efficacy of the preparation according to claim 1 in the treatment of all claimed medical disorders – could be attained. The application did not contain an example according to the invention and no plausible cause-effect relationship was provided. In addition, the involvement of the muscarinic M1 receptor in the claimed disorders had not been rendered sufficiently plausible in the application itself. The subsequently filed documents D47 and D48 should therefore be disregarded. Moreover, D47 and D48 could not be used to demonstrate an effect on the muscarinic M1 receptor because, firstly, the PC12 cells which were used in the studies of D47 and D48 expressed three different subtypes of muscarinic receptors (M1, M2 and M4) and only 3% were of the M1 subtype. Secondly, oxotremorine was an unspecific muscarinic agonist. Furthermore, even if an improved effect on the muscarinic M1 receptor could be acknowledged, therapeutic efficacy of the preparation to be used according to claim 1 as granted in the treatment of all claimed disorders could not be accepted. There was no plausible relationship between the muscarinic M1 receptor and the claimed disorders, except for Alzheimer's disease. For most of the other disorders an improvement of cholinergic neurotransmission was even contra-indicated.

It could be argued, as it was by the opposition division in the decision under appeal, that the therapeutic efficacy of the preparation to be used according to claim 1 as granted for the treatment of

all claimed disorders was rendered plausible by the state of the art (e.g. D3, D4, D5, D21, D22 and D26), although not in connection with an effect on the muscarinic M1 receptor. However, this meant that any specific effect on the muscarinic M1 receptor was irrelevant in the assessment of inventive step.

The application gave no indication of the uridine or cytidine concentrations that needed to be applied for the claimed effect to be achieved, which meant that trace amounts of these components could be present. Trace amounts, however, would be ineffective.

No meaningful interpretation of the expression "at least 50 mg nucleobases, including uridine and cytidine" was possible. The object of obtaining nucleobases, including uridine and cytidine, could therefore not be achieved and the skilled person was confronted with an unsolvable problem under Article 83 EPC.

- Inventive step

Document D26 was the closest prior art. It disclosed preparations comprising components i) and ii) to be used in the treatment of the same disorders as claim 1 as granted. The distinguishing feature was the presence of uridine and cytidine. No effect which had its origin in the distinguishing feature had been shown. The problem to be solved was therefore the provision of a further treatment of the claimed disorders. The solution was obvious in view of the disclosure in document D21.

Documents D47 and D48 could not demonstrate a specific effect on the muscarinic M1 receptor, because the PC12

cells expressed different receptor subtypes. At best, an effect on the muscarinic M1, M2 and M4 receptors could be deduced, which however, did not plausibly demonstrate efficacy in all claimed therapeutic uses. Irrespective of this deficiency, documents D47 and D48 could not demonstrate a synergistic effect because essential control experiments were missing, for example experiments with component i) or ii) alone. Furthermore, neither D47 nor D48 contained a comparison with the prior art. Conditions A and B in D47 and D48 could not be directly compared, as the effect of phospholipids on the muscarinic M1 receptor was unknown. Moreover, it was highly doubtful whether improvements on the muscarinic M1 receptor could be extrapolated to different receptors involved in different diseases. Document D53, which did not contain a comparison of a preparation according to claim 1 with the prior art, could not support D47 and D48.

Document D26 was directed to the same disorders as claim 1 as granted. It also mentioned the influence of homocysteine levels on neurotransmitters (see page 3, lines 8 to 17), which was the same problem as in the patent in suit. Document D21 was also directed to the treatment of the same disorders. Finding a more detailed underlying mechanism could not render the well-known treatment of a disorder inventive when using the same preparation and providing a further component, also known for the treatment of the same disorders, in the absence of any technical effect caused by said further component. Faced with the problem of providing a further preparation to be used in the claimed treatment, the skilled person would be prompted to combine the teaching of D26 and D21. He would have arrived at the claimed subject-matter without requiring any inventive skill.

The statement on page 8, lines 8 to 13 of D26 would not discourage the person skilled in the art from combining D26 with D21, as the teaching of D26 was not restricted to preparations consisting essentially of components i) and ii). It was even doubtful whether a content of 50 mg nucleobase would be considered an essential amount. The statement on page 11 of D26 (see lines 30 et seq.) does not discourage the skilled person from combining D26 and D21 either. This statement merely warned the skilled person that, when essential fatty acids were used, oxidation should be avoided, preferably by the use of an antioxidant.

- Admission of auxiliary request 1

This request should not be admitted into the proceedings. It could and should have been filed much earlier in the proceedings. The appellant had four years to file this request, as respondent 1's reply to the statement of grounds of appeal pointed out that auxiliary request 1 filed with the statement of grounds of appeal was not identical to auxiliary request 1 on which the decision under appeal was based. The reintroduction of the latter was not conducive to the proceedings and, in addition, could not overcome the objections that had been raised against the main request.

- Inventive step

The combination of compounds ii) was already disclosed in D26. It could not overcome the objection that the subject-matter of the main request lacked an inventive step.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted, i.e. that the oppositions be rejected, or, alternatively, that the patent be maintained in amended form on the basis of the set of claims of auxiliary request 1 as filed during the oral proceedings before the board.

XIV. Respondents 1 and 2 requested that the appeal be dismissed. They also requested that that documents D52 and D53 and auxiliary request 1 filed at the oral proceedings before the board not be admitted into the appeal proceedings.

XV. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents D52 and D53 into the appeal proceedings (Article 12(4) RPBA)

2.1 The respondents objected to the admission of documents D52 and D53 on the grounds that they were late-filed and *prima facie* not relevant.

2.2 Documents D52 and D53 were filed by the appellant with the statement of grounds of appeal. The appellant challenged the opposition division's findings on inventive step and filed these documents in an attempt to address certain aspects discussed in the decision under appeal. In particular, D52 was filed to demonstrate that the muscarinic M1 receptor was

associated with the claimed disorders, and D53 to further support the experimental evidence in documents D47 and D48.

2.3 The lack of evidence for the involvement of the muscarinic M1 receptor in the treatment of the claimed disorders other than dementia, like Alzheimer's disease, was one of the reasons why the opposition division did not acknowledge that the purported technical effect (improvement of receptor function) was achieved over the whole scope of the claims (see page 14, point 2.4.3 of the decision under appeal). This aspect emerged as an additional argument in the discussion of inventive step at the oral proceedings before the opposition division, in particular in the context of whether or not the appellant's experimental evidence (i.e. D47 and D48) could support the breadth of the claim. This issue had been raised before in the context of sufficiency of disclosure and inventive step. The appellant's arguments with regard to an improvement based on D47 and D48 did not convince the opposition division and were not taken into account in the formulation of the technical problem, leading to the revocation of the patent in suit.

In these circumstances, the board is of the opinion that the submission of document D52, filed with the statement of grounds of appeal and therefore at the earliest possible moment, was a legitimate attempt by the appellant to further support its position regarding the purported improvement. The same applies with regard to document D53, which was filed to further support the experimental data in documents D47 and D48. As an attempt to corroborate the purported improvement, documents D52 and D53 were *prima facie* relevant for the question of inventive step. Whether or not they

provided conclusive evidence was an issue to be considered in the assessment of inventive step.

2.4 Hence, the board decided that documents D52 and D53 formed part of the appeal proceedings pursuant to Article 12(4) RPBA.

Main request (patent as granted)

3. Sufficiency of disclosure (Article 100(b) EPC)

3.1 Claim 1 of the main request is directed to medical uses of a preparation comprising i) polyunsaturated fatty acids (PUFAs) comprising at least docosahexaenoic acid (DHA), ii) one or more components which have a beneficial effect on total methionine metabolism selected from the group of vitamin B12, vitamin B6, folic acid, zinc and magnesium, and iii) at least 50 mg nucleobases, including uridine or cytidine, or phosphates thereof, per daily dose. The medical uses are for Parkinson's disease, Huntington's chorea, epilepsy, schizophrenia, paranoia, depression, sleep disorders, impaired memory function, psychoses, dementia and ADHD.

3.2 According to the established jurisprudence of the boards of appeal, if a therapeutic use is to be accepted as sufficiently disclosed, the application as filed must provide some information rendering it technically plausible for the skilled person that the claimed therapeutic use is attained, or the therapeutic effect must be derivable from the prior art or common general knowledge (see e.g. T 1599/06, point 6 of the Reasons; T 609/02, point 9 of the Reasons).

3.3 According to the application, the present invention relates to a preparation for improving the action of receptors, in particular the sensitivity of receptors to neurotransmitters (see page 1, lines 4 to 5; page 9, line 31 to page 10, line 3).

Receptors can be located in the membrane of cells. They are involved in signal transmission pathways and are activated by components which bind to the receptor. A specific class of receptors are nerve cell receptors, which are controlled by neurotransmitters. Disturbances in neurotransmitter functioning due to reduced concentration of neurotransmitters or neuromodulators or reduced sensitivity of the receptor to the neurotransmitters play a role in neurological disorders, including those according to claim 1 of the main request. This was state of the art for the present application (see application page 3, line 24 to page 4, line 25; page 11, lines 29 to 32).

The application further explains that the therapeutic effect is essentially based on the influence PUFAs - in combination with component ii) inhibiting their oxidation - have on the fluidity of cell membranes, which in turn facilitates conformational changes in the receptor and receptor activation (see application page 3, line 24 to page 4, line 7; page 11, lines 29 to 32).

Nucleotides or precursors thereof, in form of RNA, uridine, cytidine or their phosphates, are mentioned in the application as potentially useful additional components because they stimulate the formation of neurotransmitters (see page 8, lines 3 to 4 and page 9, lines 19 to 25).

The invention is further illustrated by an example which demonstrates the influence of a specific diet containing components i) and components ii) on certain receptors (see page 11, line 18 and page 12, Table 2).

3.4 Based on the information and the evidence provided in the application, the board considers it technically plausible that the therapeutic use, i.e. the treatment of the claimed neurological disorders, is attained by the preparation to be used according to claim 1 as granted, which comprises PUFAs and component ii). There is no reason to assume that this changes with the presence of uridine or cytidine, which are known to stimulate the formation of neurotransmitter.

3.5 Moreover, the board notes that the use of components i) to iii), either alone or in combination, in the treatment of the claimed disorders is already known in the art. The use of PUFAs, which are major components in the brain and neural tissues and believed to play an important role in modulating the structure, fluidity and function of the cell membranes, is known in the treatment of neurological disorders such as depression, anxiety, dementia, Alzheimer's disease, schizophrenia and Parkinson's disease (see documents D4, D5, D9a, D22, D26, D31 and D33). Components ii) are known to decrease the oxidation of polyunsaturated (essential) fatty acids (see D26 and page 4, lines 9 to 25 of application as filed), thereby making the desired results of polyunsaturated fatty acid administration more likely. Components iii) are known in the art for the treatment of epilepsy, disorders involving memory decline, such as dementia, Alzheimer's disease and Huntington's disease, and mood or emotional disorders, such as depression, panic, insomnia and psychosis (see D3 and D21). None of this was contested. Hence, even in

the absence of any data in the application for a preparation comprising all three components i) to iii) (the experimental evidence in the application is limited to preparations with components i) and ii)) there are no apparent reasons, based on verifiable facts, to doubt that the claimed therapeutic uses are attained by the claimed preparation. In particular, there are no reasons to believe that the components i), ii) and iii) negatively interfered with each other, thereby rendering the claimed treatment unattainable.

3.6 The respondents' argument concerning the missing link between the muscarinic M1 receptor and disorders such as epilepsy, Parkinson's disease, Huntington's disease, schizophrenia, depression and sleep disorders and the alleged non-suitability of documents D47 and D48 to demonstrate an effect on this receptor (see point XII above) is not relevant for the question of sufficiency of disclosure concerning the invention defined in claim 1 of the main request, as no effect on the muscarinic M1 receptor is required according to this claim. It is established jurisprudence of the boards of appeal that an objection of sufficiency of disclosure cannot legitimately be based on an argument that the patent does not enable a skilled person to achieve a non-claimed technical effect (see e.g. T 1311/15, point 5.2 of the reasons; T 2001/12, points 3.2 to 3.4 of the reasons). Such an effect may, however, be relevant in the assessment of inventive step.

3.7 It was further argued that in the absence of the amount of uridine and cytidine to be used, the skilled person was unable to carry out the claimed invention. Trace, and therefore ineffective, amounts of uridine or cytidine could be present.

3.8 In the board's judgement, the absence of a precise amount of uridine or cytidine, or components i) and ii) for that matter, does not call the sufficiency of disclosure into question, as the skilled person finds sufficient guidance in the application as regards the required amounts of compounds i), ii) and iii). For uridine or cytidine, for example, the application discloses on page 9, lines 19 to 25 that at least 50 mg nucleobase, including uridine or cytidine (i.e. component ii)), corresponds, for example, to at least 2.5 g crude brewer's yeast. The respondents have not provided any evidence that justifies the conclusion that, despite the guidance provided in the application, the skilled person is faced with undue burden when attempting to put the invention into practice. In this context, it should also be noted that uridine and cytidine are not the only effective components for the claimed use.

3.9 In the written proceedings, respondent 2 also argued that the invention was insufficiently disclosed as component iii) could not be obtained for want of a meaningful interpretation of the feature "nucleobases, including uridine and cytidine". At the oral proceedings before the board, respondent 2 did not rely on this objection. For reasons of completeness, the board would like to point out that it concurs with the opposition division that this lack of clarity does not prevent the skilled person from carrying out the invention on the basis of the information provided in the application (see decision under appeal point 1.2.3 of the reasons). No reasons had been provided as to why the opposition division's findings were incorrect in this respect.

3.10 For the aforementioned reasons and in the absence of any evidence to the contrary, the board concludes that the ground of opposition under Article 100(b) EPC does not prejudice the maintenance of the patent in suit.

4. Inventive step (Article 100(a) and Article 56 EPC)

4.1 The board, in agreement with the opposition division and the parties, considers document D26 to be a suitable starting point for the assessment of inventive step.

This document relates to pharmaceutical and nutritional formulations comprising essential fatty acids (i.e. long-chain polyunsaturated fatty acids), including docosahexaenoic acid, in combination with one or more homocysteine-lowering agents, selected from vitamin B12, folic acid, a compound related to folic acid with similar biological activity and vitamin B6, and a pharmaceutically acceptable excipient (see claims 1-3 and 8, page 8, lines 4 to 26). The formulations are useful in the treatment of a variety of disorders, such as psychiatric disorders, including schizophrenia, depression and sleep disorders, and neurological or neurodegenerative disorders, including dementia, Alzheimer's, Parkinson's and Huntington's disease (see claim 15 and page 1, line 1 to page 2, lines 28, page 5, lines 14 to page 6, line 4).

4.2 It is undisputed that the preparation to be used according to claim 1 as granted differs from the preparation to be used according to D26 on account of the addition of uridine or cytidine (component iii)).

4.3 In the light of document D26, the appellant formulated the problem to be solved as the provision of a

preparation to be used in the treatment of the claimed disorders with a significantly improved (i.e. synergistic) effect on the activation of receptors involved in the claimed therapeutic uses.

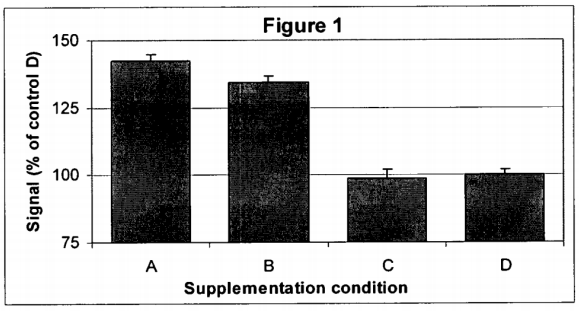
4.4 The appellant and the respondents were divided as to whether the experimental evidence on which the appellant relied in this context (see documents D47, D48 and D53) convincingly demonstrated the alleged improvement.

4.5 Document D47 relates to *in vitro* studies which examined the effects of polyunsaturated fatty acids, B vitamins and uridine nucleotide supplementation on cholinergic receptor activation. PC12 cells expressing the G protein-coupled muscarinic M1 receptor were used after 24 hours' supplementation. Oxotremorine, a muscarinic acetylcholine receptor agonist, was used to activate the receptor. Receptor activation and the resulting difference in membrane potential were measured (see D47, second paragraph).

Four different supplementation conditions were examined:

Condition	Supplementation
A	▪ PUFA's (40 µM of DHA and EPA in a ratio of 1:1) ▪ Nucleotides (10 µM of uridine monophosphate (UMP)) ▪ B vitamins (4 µg/ml folic acid, and 4 µg/ml pyridoxine)
B	▪ PUFA's (40 µM of DHA and EPA in a ratio of 1:1) ▪ Phospholipids (10 µM of PC and PS in a ratio of 1:1) ▪ B vitamins (4 µg/ml folic acid, and 4 µg/ml pyridoxine)
C	▪ Nucleotides (50 µM of CMP+UMP+IMP+GMP+AMP in a ratio of 55:20:15:15:15)
D	▪ Control medium

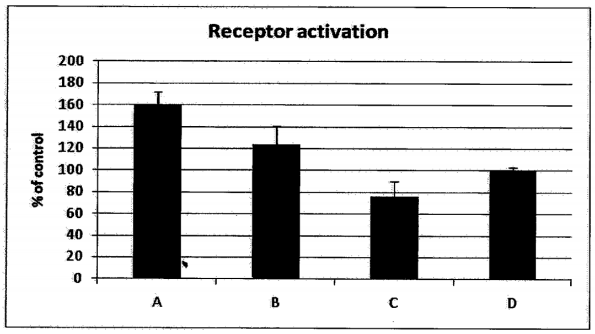
The following results were obtained:



4.6 Further *in vitro* studies in PC12 cells with oxotremorine and the following supplementation conditions are described in document D48.

	Supplementation	
A	PUFAs nucleotides B vitamins	(20 µM DHA) (50 µM uridine monophosphate (UMP)) (15 µM folic acid, and 10 µM pyridoxine)
B	PUFAs Phospholipids B vitamins	(20 µM DHA) (25 µM of PC and PS in a ratio of 1:1) (15 µM folic acid, and 10 µM pyridoxine)
C	nucleotides	(11 µM UMP + 27.5 µM CMP + 8.25 µM IMP + 8.25 µM GMP + 8.25 µM AMP)
D	control medium	

The observed results are as follows:



4.7 Concerning the alleged synergistic effect, the board concurs with the respondents that the experimental evidence provided in D47 and D48 cannot demonstrate such an effect, as vital control experiments are missing, for example supplementation with PUFAs alone (i.e. docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in D47 and DHA in document D48), with folic

acid and pyridoxine (B vitamins) alone, with phospholipids (phosphatidylcholine (PC) and phosphatidylserine (PS)) alone, with uridine monophosphate (UMP) alone, or with combinations of these compounds. In particular, there are no experiments with supplementation of PUFAs alone, which play an essential role in membrane fluidity, on which the patent in suit relies as an explanation for improved receptor activation, or, more importantly, with supplementation with PUFAs in combination with B-vitamins as taught in D26. In the absence of such experiments, in particular an experiment that truly reflects the closest prior art, no conclusion can be drawn as to whether any improvement on receptor activation, let alone a synergistic effect, is achieved.

In this context, the board also notes that the appellant did not provide any convincing explanation as to why a mixture of nucleotides was used in condition C of documents D47 and D48 as opposed to a single nucleotide (UMP) as in condition A. Even if, as argued by the appellant, the amount of UMP in the mixture used in D47 is practically identical, this does not mean that the effect of UMP is necessarily the same, irrespective of whether that compound is used alone or in combination. The board also notes that in D48 the amount of the nucleotide mixture used in condition C differs from the amount of nucleotide (UMP) used in condition A. In addition, the amount of UMP is much lower than in condition A. The same applies even if the amount of cytidine monophosphate (CMP), which according to the appellant is interchangeable with UMP, is taken into account.

4.8 The direct comparison of condition A with condition B at best allows the conclusion that the presence of 10 µg UMP in a composition comprising DHA/EPA and B vitamins or 50 µg UMP in a composition of DHA and B vitamins improves receptor activation compared with the presence of 10 µg of a mixture of phospholipids in a composition comprising DHA/EPA and B vitamins or 25 µg of a mixture of phospholipids in a composition comprising DHA and B vitamins, at least according to statements in D47 and D48 (see D47, page 2, "Results"; D48, paragraph bridging pages 2 and 3). Taking account of the standard deviation, there does not seem to be much difference between examples A and B. Whether condition A significantly improves receptor activation over D26 and whether this effect is associated with the presence of uridine (i.e. the only distinguishing feature compared with the closest prior art) is not derivable, for want of any experiments without UMP.

4.9 The appellant argued that an improved effect on receptor activation associated with uridine could nevertheless be deduced by comparing conditions A and B in D47 and D48, because phospholipids were known to contribute to the effect (see D29) and uridine, which has no effect, increased this effect even further.

4.10 The board is not convinced, in particular in the absence of any evidence which can support the appellant's assertion. Neither D47 nor D48 contains conditions from which it can be deduced that phospholipids significantly improve receptor activity over the prior art. In other words, the control experiment with PUFAs and B vitamins is missing. Document D29 is not relevant in this context as it does not contain any data, let alone data related to receptor activation.

4.11 It has also been argued that phospholipids have hardly any effect on receptor activity, which makes a direct comparison of condition A with the prior art possible (i.e. condition B). However, irrespective of the fact that this argument is inconsistent with the argument that phospholipids activate the receptor, it is equally unconvincing in the absence of any control experiments with PUFAs and B vitamins. Document D53 is not relevant in this context, as it does not contain a comparison of preparations comprising components i), ii) and iii) with preparations comprising components i) and ii). It merely shows that the addition of phosphatidylcholine (a phospholipid) does not significantly improve the effect of a composition of DHA, uridine, choline, B vitamins, vitamins E and C, selenium and EPA (see page 636, Fig. 4(c), in particular columns bc and c). In the board's judgement, this specific finding cannot be readily extrapolated to other compositions.

4.12 Fact is that the effect of phospholipids or uridine on receptor activation in compositions comprising PUFAs and B vitamins is simply not derivable from D47 and D48 in the absence of adequate control experiments.

4.13 It follows from the above considerations that the alleged advantage of the claimed invention over the prior art (i.e. improvement of receptor action and, as a consequence, improvement in the treatment of the claimed diseases) is not adequately supported by the experimental evidence on which the appellant relies. Nor has it been shown that any other effect is obtained that is not present if preparations according to D26 are used.

4.14 According to the established jurisprudence of the boards of appeal, alleged but unsupported advantages cannot be taken into account in the determination of the problem to be solved. As a consequence, the technical problem as formulated in point 4.3 above has to be reformulated in a less ambitious way. In the light of document D26, it can merely be seen as the provision of a further preparation to be used in the treatment of the claimed diseases.

The board has no reason to doubt that this problem is solved by the claimed subject-matter.

4.15 The proposed solution, i.e. the combination of components i), ii) and iii), to be used in the treatment of the claimed disorders was obvious in view of the prior art.

As indicated above, the feature that distinguishes the claimed invention from document D26 is the presence of uridine or cytidine or their phosphates (component iii)). The use of uridine or a uridine source in the treatment of the claimed disorder was, however, known in the art (see D21, page 5, lines 13 to 23, claims 16 to 21 and 28). Hence, the claimed subject-matter is merely the result of an arbitrary combination of components known *per se* for the treatment of the claimed disorders, which in the absence of any unexpected or surprising technical effect did not require any inventive skill.

4.16 The appellant argued against a combination of documents D26 and D21 on the grounds that D26 was silent on the addition of uridine or cytidine or on receptor-linked disorders and that D21 was completely silent on neurotransmitter receptor functioning and had a

different aim. Moreover, the observed synergistic effect was unexpected, even if the skilled person had considered combining the teaching of both documents.

4.17 The board is not convinced. As explained above (see points 4.8 to 4.13), a synergistic effect has not been adequately demonstrated. Therefore, the appellant's argument in this respect cannot be accepted. Indeed, no effect that is not present if a preparation according to D26 or D21 is used has been demonstrated. As regards the missing indication as to the effect on neurotransmitter receptor function, the board considers that this lack of information as to the underlying mechanism of action of each component is not relevant and would not have discouraged the skilled person, faced with the aforementioned problem, from combining the teachings of both documents, at least as long as he had no reason to believe that this combination would lead to any negative effects. The board is not aware of any such reasons and none has been provided.

4.18 As regards the allegedly different aim of D21, the board re-emphasises that D21 is directed to the same therapeutic use as both D26 and the claimed invention according to claim 1 as granted.

4.19 The appellant also argued that the skilled person would not have considered document D21 as he had no reason to believe that D21 could help promote homocysteine-lowering components. There was no reasonable expectation that uridine could further aid homocysteine metabolism. However, the problem to be solved in the light of D26 is the provision of an alternative preparation for use in the treatment of the claimed disorders. The appellant's argument as to an alleged improvement in homocysteine levels, for which there is

no evidence, is therefore not considered to be pertinent.

4.20 The appellant's argument that D26 would have discouraged the skilled person from adding uridine is equally unconvincing. The passage on which the appellant relied in this context mentions that the administration of polyunsaturated fatty acids in a formulation which has no significant amounts of other micronutrients is preferred, and that the formulation preferably consists of polyunsaturated fatty acids and the homocysteine-lowering agent. However, the teaching in D26 is not limited in this respect (see the expression "comprising" in claim 1 and claim 14, according to which certain vitamins (i.e. micronutrients) can be present). A technical prejudice, in the sense that the skilled person would not have considered the addition of any further component, is not derivable from document D26. Similarly, the board does not consider the statement on page 11 to be a prejudice against the addition of uridine. Said statement merely warns the skilled person that fatty acids, which are a mandatory component of the preparation disclosed in D26, are easily oxidised and therefore suggests the use of an anti-oxidant.

4.21 In view of the above, the board concurs with the respondents that the skilled person would have arrived at the claimed subject-matter in an obvious way by combining the teaching of D26 and D21. No inventive skill was required.

4.22 Hence, the board concludes that the ground for opposition pursuant to Article 100(a) in conjunction with Article 56 EPC prejudices the maintenance of the patent in suit.

Auxiliary request 1

5. Admission into the appeal proceedings (Article 13 RPBA)

5.1 The set of claims of auxiliary request 1 was filed at the oral proceedings before the board. It is identical to the set of claims of auxiliary request 1 on which the decision under appeal was based. The appellant justified the filing of this request on its true intention to maintain this request, as expressed in the statement of grounds of appeal (see page 3, lines 13 to 18), and the realisation that even the corrected version of auxiliary request 1 as filed with the letter of 19 June 2019 did not reflect this intention in every detail.

The respondents objected to the admission of auxiliary request 1 into the appeal proceedings.

5.2 The board shares the respondents' view that auxiliary request 1 could have been filed at an earlier stage in the appeal proceedings, as respondent 1's reply to the statement of grounds of appeal had made the appellant aware of the fact that auxiliary request 1 accompanying the statement of grounds of appeal was not identical to auxiliary request 1 on which the decision under appeal was based. However, auxiliary request 1 was not based on any new subject-matter which could have either surprised the respondents or unduly delayed the appeal proceedings. Furthermore, auxiliary request 1 did not raise any new complex technical and legal issues that could not have been properly dealt with by the board or the respondents at the oral proceedings.

5.3 Hence, exercising its discretion under Article 13(1) and (3) RPBA, the board decided to admit auxiliary request 1 into the proceedings.

6. Inventive step (Article 56 EPC)

6.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that component ii) contains a combination of vitamin B12, vitamin B6 and folic acid.

6.2 The amendment made in auxiliary request 1 does not alter the above assessment of inventive step. The use of a combination of vitamin B12, vitamin B6 and folic acid is already taught in D26 (see examples 5 to 8) and has not been shown to be associated with any particular technical effect. Indeed, the parties did not submit any inventive-step arguments specific to auxiliary request 1. Therefore, the board concludes that auxiliary request 1 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

M. Schalow A. Lindner

Decision electronically authenticated