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Datasheet for the decision of 19 March 2021

Case Number: T 1214/17 - 3.3.07

Application Number: 09716304.2

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Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL SOLUTIONS, PROCESS OF PREPARATION AND THERAPEUTIC USES

Patent Proprietor:
UCB Pharma, S.A.

Opponents:
Hollatz, Christian
Generics [UK] Limited (trading as Mylan)

Headword:
Pharmaceutical solutions/UCB PHARMA

Relevant legal provisions:
EPC R. 152, 116(1)
EPC Art. 114(2), 54, 56
RPBA Art. 12

Keyword:
Authorisation - filing of authorisation
Late submitted material - document admitted (no)
Novelty - (yes)
Inventive step - (no)

Decisions cited:
T 1744/09, T 0382/03, T 0637/09, T 0924/17, T 0066/14

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Case Number: T 1214/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 March 2021

Appellant: (Patent Proprietor)	UCB Pharma, S.A. 60, Allée de la Recherche 1070 Brussels (BE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent 1)	Hollatz, Christian Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Opponent 2)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 24 March 2017 revoking European patent No. 2273975 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

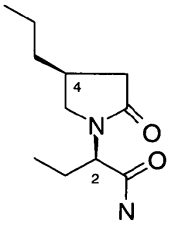
Summary of Facts and Submissions

I. European patent 2 273 975 (hereinafter "the patent") was granted on the basis of six claims.

The independent claim 1 as granted related to:

"A stable solution of a pharmaceutical compound being (2S)-2-{(4R)-2-oxo-4-propyl-pyrrolidin-1-yl)} butanamide, characterized in that it has a pH value of between 4.5 and 6.5."

This pharmaceutical compound is further referred to as brivaracetam. It has the following structure:



Brivaracetam

II. Two oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

The appeal was filed by the proprietor (hereinafter "appellant") against the decision by the opposition division to revoke the patent.

The decision by the opposition division was based on the patent as granted (main request), auxiliary requests 1-14 filed on 12 August 2015 and auxiliary requests 15-16 filed on 21 December 2016.

III. In the present decision, reference is made to the following documents:

D2: L. Lachman et al., "The Theory and Practice of Industrial Pharmacy", Varghese Publishing House, Bombay, 3" edition, 1987, pages 190-193, 764
D3: H. Feitkamp et al., "Pharmazeutische Qualitatskontrolle", Georg Thieme Verlag Stuttgart New York, 1983, pages 502-504
D4: EP1731149A1
D5: Declaration of F. Schenkel and D. Clicq of March 22, 2012, filed on 13 April 2013 during prosecution of the opposed patent
D6: Keppra® (levetiracetam) injection leaflet, 2006
D7: H. Theuer et al. "Stabilitätsuntersuchungen von Piracetam-lnfusionslosungen", Pharmazeutische Zeitung., 1987, 132, pages 1024-1029
D10A : Remington's Pharmaceutical Sciences, 1985, pages 1478-1486
D11: Plumer's Principles and Practice of Intravenous Therapy, Weinstein, 2007, page 126
D12: Handbook on Injectable Drugs, 2011 , 16th edition, L.A. Trissel, pages 419, 476, 489, 501, 615-616, 959, 1254, 1262, 1401, 1503
D15: Decision of the Board of Appeal of the USPTO dated 08.11.2016 in the equivalent US application US 2011/021786 A1
D16: D. Voet, J. G. Voet "Biochemie", VCH, Verlagsgesellschaft mbH, Weinheim, 1994, pages 36-39

D17: R. Voigt 'Pharmazeutische Technologie', Deutscher Apotheker Verlag, Stuttgart, 2006, pages 569-573 and 579-580
D18: Christian Wolf, "Dynamic Stereochemistry of Chiral Compounds, Principles and Applications", The Royal Society of Chemistry, 2008, pages 68-69.
D19: Riegelman, S., "The Effect of Surfactants on Drug Stability I", Journal of the American Pharmaceutical Association, Vol. 49, No.6, 1960, pages 339-343
D20: Loftsson et al., "Pharmaceutical Applications of Cyclodextrins", Journal of Pharmaceutical Sciences, Vol. 85, No. 10, 1996, pages 1017-1025
D21: Snape, Timothy et al., "Understanding the chemical basis of drug stability and degradation", The Pharmaceutical Journal, Vol. 285, 2010, p416
D22: Test results filed by patentee with letter of 21.12.2016, (embedded on pages 4-5 of the letter)
D24: Europäisches Arnzneibuch, 4th edition, Volume 1, pages 27-28 by the appellant patent-proprietor with the letter of 14 March 2019.
D25: Stability Report Keppra IV 500 mg/mL

IV. The opposition division was of the opinion that the subject-matter of claim 1 as granted differed from the disclosure in document D4 in the definition of the pH in the range of 4.5 to 6.5. In view of the experimental results reported in tables 1-3 of the patent and the post-published documents D5 and D22 the technical problem to be solved was formulated as the provision of liquid solutions of brivaracetam which offer stability against hydrolysis and epimerisation. The provision of brivaracetam in solutions with a pH of 4.5 to 6.5 was considered obvious in view of common general knowledge as represented in document D2 as well as in view of document D7 taking account of the common general

knowledge as represented in document D17. The subject-matter of the auxiliary requests 1-16 did not involve an inventive step for similar reasons as the patent as granted. The opposition division did not admit document D15 for lack of relevance.

V. In the statement setting out the grounds of appeal the appellant relied on the patent as granted and auxiliary requests 1-16 corresponding to the requests on which the appealed decision was based.

Claim 1 of auxiliary request 1 corresponds to claim 1 as granted except that it defines the pH values more narrowly by the feature: "characterized in that the pH values are between 4.5 and 6.0."

Claim 1 of auxiliary request 2 corresponds to claim 1 of auxiliary request 1 with additional definition of the feature: "and that the amount by weight of the pharmaceutical compound is in the range of 0.1 mg to 50 mg per ml."

Claim 1 of auxiliary request 3 corresponds to claim 1 as granted except that it defines the pH values still more narrowly by the feature: "characterized in that the pH values are between 5.0 and 6.0."

Claim 1 of auxiliary request 4 corresponds to claim 1 of auxiliary request 3 with additional definition of the feature: "and that the amount by weight of the pharmaceutical compound is in the range of 0.1 mg to 50 mg per ml."

Claim 1 of auxiliary request 5 corresponds to claim 1 as granted except that it defines the pH values even

more narrowly by the feature: "characterized in that is has a pH value of 5.5 +/- 0.2."

Claim 1 of auxiliary request 6 corresponds to claim 1 of auxiliary request 5 with additional definition of the feature: "and that the amount by weight of the pharmaceutical compound is in the range of 0.1 mg to 50 mg per ml."

The independent claims of auxiliary requests 7-13 correspond respectively to the the independent claim as granted and the independent claims of auxiliary requests 1-6 except that the the solution is defined as "aqueous solution".

Claim 1 of auxiliary request 14 corresponds to claim 1 as granted with additional definition of the feature: "and it contains less than 0.2 % (by weight) of impurities."

Claim 1 of auxiliary request 15 relates to: "Use of a solution of a pharmaceutical compound being (2S)-2-{(4R)-2-oxo-4-propyl-pyrrolidin-1-yl)} butanamide, characterized in that it has a pH value of between 4.5 and 6.5, for stabilizing the pharmaceutical compound against epimerisation."

Claim 1 of auxiliary request 16 corresponds to claim 1 of auxiliary request 15 except that it defines the solution as "aqueous solution".

VI. In a communication pursuant to Article 15(1) RPBA issued on 08 October 2020 the Board expressed *inter alia* the preliminary opinion that the subject-matter defined in claim 1 of the patent seemed to be new over

document D4, but did not seem to involve an inventive step in view of document D4 as closest prior art.

VII. With the consent of the parties oral proceedings were held on 19 March 2021 in the form of a videoconference. The oral proceedings were attended by the appellant and the respondent (opponent 1). The respondent (opponent 2) had announced not to attend.

VIII. The arguments of the appellant relevant to the present decision can be summerized as follows:

(a) The decision of the opposition division was invalid due to a substantial procedural violation in relation to Rule 152(6) EPC. No authorization had been presented by the representatives attending the oral proceedings before the opposition division for the respondent (opponent 1). Following a change in the representation such authorization was required in accordance with the Decision of the President of the European patent Office dated 12 July 2007 on the filing of authorisations" (Special Edition No. 3, OJ EPO 2007, 128).

(b) The opposition division properly exercised their discretion not admitting document D15 for lack of relevance.

(c) The subject-matter of claim 1 as granted was new over document D4, which did not disclose brivaracetam solutions having a pH in the defined range. The mention of buffers for formulation with brivaracetam in paragraph [0021] of document D4 did not necessarily imply a pH between 4.5 and 6.5, as was evident from document D24.

(d) Document D4 represented the closest prior art. This document did not describe brivaracetam solutions having a pH between 4.5 and 6.5 as claimed in the patent. Moreover, document D4 only described a concept for pharmaceutical solutions of brivaracetam, which was still to be developed.

According to the teaching of the patent (paragraphs [0011]-[0012]) the pH range of 4.5 to 6.5 provided stability against hydrolysis and epimerisation. This teaching was supported by the experimental results reported in example 1 of the patent and the documents D5 and D22. The problem to be solved was to be seen in the provision of a liquid pharmaceutical composition of brivaracetam which afforded stability of brivaracetam against hydrolysis and epimerisation.

The subject-matter of the patent was not obvious to the skilled person. Results of any initial solution stability studies on preformulations carried out in line with documents D2 or D3 would only represent a starting point for a research program for the development of actual pharmaceutical formulations. Such development still had to take account of further considerations regarding pharmacologic activity, physiological acceptability and compatibility with further components, as was explained in documents D10A and D17 and illustrated in document D12 with respect to Diltiazem. Document D4 presented in this context only a concept of pharmaceutical compositions with mention of solids and liquids on equal level and without a pointer to the claimed solution. As further illustrated by documents D10 and D19-D21 the skilled person had many options to explore.

The effect of the pH on stability against epimerisation was according to document D17 not predictable. Moreover document D18 did not suggest that brivaracetam was at risk of epimerisation, whereas document D6 and D25 actually suggested its stability towards epimerisation.

The simplicity of the claimed solution presented a further indication of an inventive step.

Similar arguments applied *a fortiori* with respect to auxiliary requests 1-14.

The claims of auxiliary requests 15 and 16 were specifically aimed at the utility of the defined solution for stabilization of brivaracetam against epimerisation. As the susceptibility of brivaracetam to epimerisation had not been previously described, the inventive merit of this subject-matter was further supported by the recognition of the problem of epimerisation.

IX. The arguments of the respondents relevant to the present decision can be summerized as follows:

(a) The representatives of the respondent (opponent 1) legitimately attended the oral proceedings before the opposition division of 21 February 2017 on the the basis of their authorization of 23 December 2016 filed on 28 June 2017.

(b) Document D15 was filed within the period set by the opposition division under Rule 116 EPC for filing submissions and shortly after it had become available. It was prima facie relevant because it

related to a decision by the USPTO concerning the equivalent US patent application and confirmed obviousness of an epimerically stable solution of brivarcetam with a pH between 4.5-6.5 in view of documents D4 and D7.

(c) Document D4 already described in paragraph [0021] the use of acetate and citrate buffers to formulate pharmaceutical compositions comprising brivaracetam. The patent itself indicated in paragraph [0022] that the use of these buffers allowed for optimal results. The skilled person would seriously contemplate to apply the pH range of 4.5-6-5, as this pH range was not unusual for these buffers.

(d) Document D4 represented the closest prior art. The subject-matter of claim 1 of the patent as granted could only differ from this prior art in the definition of the specific pH range. The appellant's submission, that document D4 only described a yet to be developed concept for pharmaceutical solutions of brivaracetam, should not to be admitted, as it was first raised during the oral proceedings. In any case, document D4 already described compositions to be used in therapy. Moreover the claims of the patent were not limited to pharmaceutical compositions.

The patent mentioned in paragraph [0011] degradation products as possibly resulting from hydrolysis and/or epimerisation as well as oxidation and only reported experimental results of stabilisation with respect to degradation products in general. The skilled person's realistic objective would only concern the provision of a

pharmaceutical composition which displays overall stability. Results concerning the stabilisation with respect to specifically hydrolysis and epimerisation were first presented in the subsequently filed documents D5 and D22 and should not be relied upon in the formulation of the problem to be solved.

On the basis of common knowledge represented in documents D2, D3, D10A and D17 the skilled person would routinely establish a pH stability profile for brivaracetam and thereby arrive at the claimed solution in defined pH range. Document D4 actually provided a pointer towards such pH mentioning acetates as suitable buffers. Moreover, such pH range corresponded to the most common pH values for intravenous formulations as mentioned in document D11. Once the pH range for optimal stability had been revealed by routine investigation, no particular difficulty prevented the skilled person from preparing the stable brivaracetam solutions as claimed.

According to document D17 hydrolysis and epimerisation were pH dependent degradation processes. In view of document D18 the skilled person would be aware that brivaracetam, an amide derivative of an amino acid, was at risk of epimerisation. Documents D6 and D25 did not teach away from this risk. In establishing the pH stability profile of brivaracetam the skilled person would therefore have taken account of the degradation of brivaracetam by hydrolysis and epimerisation using standard analytical methods. The skilled person would thus have arrived at the claimed subject-matter in an obvious manner even if

the problem to be solved were considered to be directed to the provision of stability against hydrolysis and epimerisation.

The same considerations applied with respect to auxiliary request 1-14. The same considerations also applied with respect to auxiliary requests 15-16, in as far as these requests were admitted.

X. The appellant requested that the decision under appeal be set aside and that the case be remitted to the first instance with the order to schedule oral proceedings, that the appeal fee be reimbursed and that respondent (opponent 1) be ordered to bear the appellant's costs incurred in relation to the oral proceedings before the opposition division of 21 February 2017. Subsidiarily, the appellant requested that the patent be maintained as granted or as amended on the basis of auxiliary requests 1-16 submitted with the grounds of appeal filed on 2 August 2017, which correspond to auxiliary requests 1-16 underlying the appealed decision.

XI. The respondent (opponent 1) requested that the appeal be dismissed, that document D15 be admitted into the proceedings and that auxiliary requests 15 and 16 not be admitted into the proceedings.

The respondent (opponent 2) requested the patent to be revoked and thus that the appeal be dismissed.

Reasons for the Decision

1. Reclamation of a substantial procedural violation

The Board observes that the attendance at the oral proceedings held on 21 February 2017 by the

professional representatives Mr. Fachini and Dr. Benito-Garagorri on behalf of the respondent (opponent 1) had been announced by the the authorized representative, Dr. Bernd Aechter, in his letter of 19 December 2016. The authorizations naming these professional representatives, who were not members of the same association as Dr. Bernd Aechter, were filed on 28 June 2017 and are dated 23 December 2016.

In its communication pursuant to Article 15(1) RPBA the Board indicated that in view of the authorisations submitted by the respondent (opponent 1) on 28 June 2017, it was satisfied that Mr. Fachini and Dr. Benito-Garagorri were authorized to represent the respondent (opponent 1) as from 23 December 2016, and could validly do so at the oral proceedings held on 21 February 2017. In this regard, reference was made to the analyse with respect to the provisions of Rule 152 EPC and the Decision of the President of the European patent Office dated 12 July 2007 on the "filing of authorisations" (Special Edition No. 3, OJ EPO 2007, 128) in the decisions T 1744/09 (points 1.7-1.9), T 382/03 (points 5.4-5.8), T 637/09 (point 1) and T 924/17 (points 1-2).

No substantive arguments were submitted by the appellant in response to the preliminary opinion expressed by the Board in its communication. Accordingly, the Board does not recognize any substantial procedural violation associated with the decision under appeal.

Since no procedural violation occurred, the appellant's requests for remittal and reimbursement of the appeal fee as well as the request for respondent (opponent 1) to be ordered to bear the appellant's costs incurred in

relation to the oral proceedings before the opposition division lack a legal basis and are therefore also rejected.

2. Admission of document D15

2.1 Document D15 was filed by the respondent (opponent 1) within the period set by the opposition division under Rule 116 EPC, but after expiry of the opposition period. Document D15 became available only after expiry of the opposition period. It concerned a decision of the Board of Appeal of the USPTO on an equivalent US application.

In accordance with T 0066/14 (see reasons 2.3-2.4) evidence first submitted by an opponent after the expiry of the nine-month period under Article 99(1) EPC, may in principle be regarded as late for the purpose of Article 114(2) EPC, unless the subject of the proceedings has changed. In the present case no such change had occurred. The Board further observes that decisions from the USPTO do generally not affect the instances of the EPO and that the particular decision in document D15 relied on prior art documents D4 and D7, which were already on file before the opposition.

The opposition division's refusal to admit document D15 in view of its late filing and lack of relevance was therefore not based on the wrong principles and was not arbitrary or unreasonable. The Board thus finds no ground for overruling the opposition division's discretionary decision in this matter (Article 25(2) RPBA 2020, Article 12(4) RPBA 2007).

3. Claim 1 as granted

3.1 Novelty

Document D4 describes compositions comprising brivaracetam, which may be in the form of oral solutions or aqueous parenteral solutions and which may optionally contain buffering agents such as acetates, citrates or phosphates (see paragraphs [0017] to [0021]).

The Board is of the opinion, that document D4 does not disclose solutions having a pH in the range of 4.5-6.5 as defined in claim 1 of the patent as granted. Such values are not explicitly mentioned in document D4 and no such values can be implicitly derived from this document. Document D11 may indicate that intravenous fluids usually have a pH in the range of 3.5-6.2 (see D11, page 126, first paragraph). However, from the term "usually" in document D11 itself it is already evident that intravenous solutions do not necessarily have a pH in the range of 4.5-6.5. This is further confirmed by the list of fluids for intravenous administration with a pH outside this range in document D12. Relevant values are also not directly and unambiguously derivable from the mention of acetate, citrate or phosphate buffers in document D4 (see paragraph [0021]). Such buffers may well be used in solutions with a pH outside the claimed range of 4.5-6.5 as shown in document D24 (table 2.2.3-2) and document D16 (figure 2-9). The argument that the skilled person would on the basis of document D4 "seriously contemplate" working in the pH range of 4.5-6.5 is therefore considered speculative and thus not convincing.

The novelty of claim 1 of the patent as granted is therefore acknowledged.

3.2 Inventive step

3.2.1 The identification of document D4 in the decision under appeal as closest prior art is not in dispute.

For the reason set out in item 1.1 above, the Board takes the view that the brivaracetam solution as defined in the claims of the patent as granted differs from the solutions described in document D4 in the feature that it has a pH value between 4.5 and 6.5.

During the oral proceedings the appellant argued that that document D4 only described a concept for pharmaceutical compostions, but failed to disclose actual pharmaceutical solutions of brivaracetam. The Board considers this argument as a legitimate development of the arguments previously submitted in writing and thus admitted it in the proceedings. At the same time the Board does not consider this argument convincing, as document D4 clearly discloses compositions for a particular therapeutic use and referred explicitly to pharmaceutical compositions (see D4 paragraph [0019]).

3.2.2 The patent as granted mentions in paragraph [0011] that aqueous solutions of 2-oxo-1-pyrrolidine derivatives were found to be partially unstable in stability storage tests, during which epimerisation and/or amide hydrolysis as well as oxidation occurred with detection of hydroxamide and hydroxyacid impurities.

The patent presents in example 1 experimental results concerning the stability of brivaracetam solutions at

different pH values (see paragraphs [0040] to [0050], Tables 1-3). The initial pH of the tested brivaracetam solutions varied from 4.6 to 6.2. The "sum of all degradation products detected" after 2, 4 and 10 weeks storage at temperatures from 25-80°C is reported. The amount of degradation products following storage at 25° remained at 0.0% for up to 10 weeks.

Document D5 presents experimental results concerning the chiral stability of brivaracetam solutions. After 2 weeks storage at 25°C significant formation (1,75%) of the 2R,4R stereoisomer occurs in a basic solution with a pH of 11. No such formation occurred in acid solutions with pH values of 1 or 6 (see D5 Table 1). Moreover, in solutions with a pH ranging from 4.5-6.0 the lowest formation of the 2R,4R stereoisomer after 4 weeks of storage at 80°C occurred at pH 4.5 (see D5 Table 2).

Document D22 presents further experimental results regarding the stability of brivaracetam solutions of different concentrations (0,5 and 20mg/ml) at pH values ranging from less than 2 to above 8. The stability against hydrolysis and epimerisation during 2 weeks storage at 60° or 80°C was tested. Maximum stability is reported for solutions with a pH between 4.5 and 6.5 (see pages 4-5).

The results from Tables 1-3 of the patent as well as the results reported in documents D5 and D22 substantiate that enhanced stability of brivaracetam, including stability against epimerisation, occurs in solutions with a pH between 4.5 and 6.5.

Having regard to the above mentioned paragraph [0011] of the granted patent, the Board takes the view that

the information in the post-published documents D5 and D22 results from experiments, which merely implement and confirm the teaching of the patent. This information may therefore be taken into account in the assessment of inventive step, in particular the formulation of the problem to be solved.

In this context the Board observes that the two prominent chiral centers in the structure of brivaracetam give rise to realistic concerns of possible epimerisation, in view of which the reported stability against epimerisation in the defined pH range cannot to be regarded as a mere bonus effect.

In view of the results presented in Tables 1-3 of the patent as well as the results reported documents D5 and D22 the Board agrees with the appellant that the objective problem to be solved is to be seen in the provision of a liquid pharmaceutical composition containing brivaracetam which allows stabilisation of brivaracetam against hydrolysis and epimerisation.

3.2.3 It has not been disputed that documents D2, D3, D10A, D11, D16, D17 and D18 represent common general knowledge.

Document D2 states that preformulation stability studies involving experiments on solutions and the solid state represent usually the first quantitative assessment of chemical stability to be performed in the development of a new drug (see page 190, left column). Such studies on solutions include the investigation of effects of pH involving the generation of a complete pH-rate profile to identify the pH of maximum stability (see D2, page 191, under "Solution Stability"; page 192, left column 5th paragraph and figure 8-22; page

764, right column). If a compound is found to be sufficiently stable, liquid formation development may start at once (see D2, page 193, left column).

Document D3 states that during preformulation studies the stability of active agents in buffered solutions is to be determined to establish the pH optimum (see page 503, third paragraph under "Haltbarkeitsprüfung...").

Document D10A mentions hydrolysis and racemization amongst others as causes of drug deterioration (see page 1479, left column under "Product Stability") and states that the stability program for solutions should include the study of pH changes (see page 1480, left column, third paragraph under "Solutions"). The document further mentions that drugs with ester or amide linkage are prone to pH dependent hydrolysis, that sometimes the optimum for pH stability is not optimal for pharmacological activity, that buffers are used when small changes in pH are expected to cause major degradation of the active ingredient and that further measures (reduction of water, chemical modification, and use of surfactants) may be used to stabilize drugs (see bridging section pages 1481-1482 under "Hydrolysis").

Document D11 states that the pH for intravenous fluids usually ranges from 3.5-6.2 (see page 126, first paragraph).

Document D16 discusses the basics of pH stabilisation by buffers and presents the buffering ranges for acetate and phosphate buffers (see page 37, in particular figure 2-9).

Document D17 states that pH adjustment represents an important measure for stabilisation of hydrolytically unstable systems (see page 571, left column), but that the pH of maximum stability is often not practical for the final composition in view of physiological suitability, solubility and efficacy concerns and compatibility with further ingredients. The document further states that racemization reactions are pH dependent, that no general statements as to pH-stability relations are possible and that the optimum pH for minimal racemization of a given drug needs to be empirically determined (see page 579, section 26.4.4.2).

Document D18 states that amino acids undergo base and acid catalyzed racemization and that the rate of conversion is increased by several factors, including derivatisation to amides and esters (see D18, bridging paragraph page 68-69).

3.2.4 In view of common knowledge as illustrated by documents D10A and D17 (see passages mentioned in section 3.4.3 above) the skilled person who starts from the aqueous solutions described in document D4 is aware of potential pH related stability issues with brivaracetam in view of its amide functional groups and its two chiral centers. As brivaracetam can be regarded as an amino acid derivative in which the carboxylic acid group is transformed to an amide and the amino group to a cyclic amide, the concern regarding epimerisation of brivaracetam is further based on common knowledge as represented in document D18 (see passage mentioned in section 3.4.3 above). The skilled person would therefore be motivated to specifically consider degradation by hydrolysis and epimerisation when carrying out routine investigations in line with

documents D2 , D3 and D10A (see passages mentioned in section 3.4.3 above) to establish a pH stability profile for brivaracetam.

The Board agrees with the respondents, that document D6 does not teach away from consideration of degradation by racemisation. The reference in document D6 to the absence of enantiomeric interconversion of levetiracetam or its major metabolite (see page 3 under "Metabolism", last sentence) relates to such absence in the context of metabolism within the frame of its 7 hour plasma half-life (see page 3 under "Elimination", first sentence). Such short term metabolic stability is not indicative for stability upon storage. The enantiomeric stability of the commercially available formulation of levetiracetam of document D6, which is confirmed in document D25, cannot be abstracted from the pH of this formulation. The pH value of 5.5 of the formulation in document D6 rather points in the direction of the claimed subject-matter than that it teaches way therefrom (see D6, page 1 paragraph 4).

In this context the Board further finds no indication that the determination of expected degradation products, for instance by chiral HPLC, amounts to undue burden. In fact, the patent provides in this respect no specific instructions and thereby relies on the general availability of relevant procedures.

The Board acknowledges that for instance from documents D10A, D19, D20 and D21 the skilled person may have been aware of alternative approaches for stabilizing active agents to be administered in the form of in solutions. However, in view of the common knowledge in the above mentioned documents D2, D3 and D10A such approaches are

secondary to the initial routine investigation of the pH stability profile.

The circumstance that the actual position of the pH optimum may not have been predictable, as indicated in document D17 in relation to epimerisation (see page 579, under 26.4.4.2), is not considered supportive of an inventive step, as the position of the optimum was bound to be determined in the initial routine investigations regarding the stability of brivaracetam solutions.

The possibility that the optimum stability of an active agent may occur at a pH value which requires a compromise in view of other practical concerns does not deprive the skilled person from the motivation to establish the pH stability profile, as he would be aware of this possibility from the same source of common knowledge that still suggests to carry out the initial investigations into the pH stability profile (see D10A page 1482, left column, second paragraph).

Accordingly, when faced with the problem of providing a liquid pharmaceutical composition containing brivaracetam which allows stabilisation of brivaracetam against hydrolysis and epimerisation the skilled person would be motivated to carry out routine investigations for determining the pH stability profile revealing the optimal pH range as defined in claim 1 as granted.

Starting from the teaching of document D4 no particular difficulty hindered the skilled person from formulating stable brivaracetam solutions by adjusting the pH to the optimal range determined by routine investigation. To the contrary, this pH range corresponds to the most common pH values for intravenous formulations as

reported in document D11. Moreover, having regard to the typical buffering range of acetates as described in document D16 the reference to acetates as suitable buffers in document D4 already pointed in the direction of the relevant pH range. In fact, the patent makes no reference to any such difficulty to be overcome and itself essentially relies on experiments for establishing a pH stability profile in support of the claimed subject-matter.

Accordingly, the Board concludes that the subject-matter of claim 1 as granted does not involve an inventive step.

4. Auxiliary requests 1-16

4.1 The independent claims of auxiliary requests 1, 3 and 5 more specifically define the pH of the defined brivaracetam solutions as between 4.5 and 6.0, between 5.0-6.0 or 5.5 +/- 0.2. As these values would result from the same routine experiments for establishing a pH stability profile of brivaracetam as discussed in the context of the main request, the very same considerations lead to the conclusion that the subject-matter of auxiliary requests 1, 3 and 5 lacks an inventive step.

4.2 The independent claims of auxiliary requests 2, 4 and 6 more specifically define with respect to auxiliary requests 1, 3 and 5 that the amount of brivaracetam ranges from 0.1-50 mg. These amounts are in line with the therapeutically effective amounts indicated in document D4 (see paragraph [0008]) and do therefore not contribute to any inventive merit.

4.3 The independent claims of auxiliary requests 7-13 additionally define with respect to the independent claim as granted and the independent claims of auxiliary requests 1-6 that the solution is aqueous. No additional distinction with respect to document D4 is thereby defined, such that the subject-matter of auxiliary requests 7-13 is to be denied an inventive step for the same reasons as set out for the preceding requests.

4.4 The independent claim of auxiliary request 14 additionally defines that the solution contains less than 0.2% by weight of impurities. As impurities in solutions of pharmaceutical compounds are obviously undesirable and no particular argument has been relied upon by the appellant with respect to the defined level of impurities, the additional feature of auxiliary request 14 is not considered to support an inventive step.

4.5 The respondent does not substantiate any reason why the discretionary decision of the opposition division to admit auxiliary requests 15 and 16 was based on the wrong principles or was arbitrary or unreasonable. The Board thus finds no ground for overruling the opposition division's discretionary decision in this matter.

The independent claim of auxiliary request 15 is directed to the use of a solution of brivaracetam, characterized in that it has a pH value of between 4.5 and 6.5, for stabilizing the pharmaceutical compound against epimerisation. The independent claim of auxiliary request 16 additionally defines the solution as aqueous.

As explained in the context of the main request the Board takes the view that starting from document D4 the skilled person would carry out routine investigations to determine the optimum pH for stability of brivaracetam taking account of its degradation by hydrolysis and epimerisation. Such investigations would reveal the information that epimerisation of brivaracetam is impeded at the defined pH values. On the basis of such information the skilled person would as a matter of obviousness use solutions of brivaracetam with the pH in the defined range to stabilize brivaracetam against epimerisation.

As already set out in relation to the main request the risk of epimerisation of brivaracetam was evident from its structure taking account of the common knowledge as presented in document D18. Therefore no inventive merit can be derived from the recognition of the problem of epimerisation of brivaracetam.

Accordingly, the Board concludes that the utility specifically aimed at stabilizing brivaracetam against epimerisation as defined in accordance with auxiliary requests 15 and 16 does not involve an inventive step.

Order

For these reasons it is decided that:

5. The appeal is dismissed

6. The requests of the appellant that the appeal fee be reimbursed and that the respondent be ordered to bear the appellant's costs incurred in relation to the oral proceedings before the opposition division are rejected.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated