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Datasheet for the decision of 14 April 2016

Case Number: T 2277/14 - 3.3.07

Application Number: 04753925.9

Publication Number: 1644019

IPC: A61K38/00, A61K47/48, A61P25/00

Language of the proceedings: EN

Title of invention:
ABUSE RESISTANT AMPHETAMINE COMPOUNDS

Patent Proprietor:
Shire LLC

Opponents:
JOHNSON MATTHEY PUBLIC LIMITED COMPANY
Generics [UK] Limited
Hexal AG

Headword:
ABUSE RESISTANT AMPHETAMINE COMPOUNDS/Shire LLC

Relevant legal provisions:
EPC Art. 100(b), 54, 56, 84, 123(2)
RPBA Art. 12(4)

Keyword:
Main request - amendments (no)
Auxiliayr request 1 - amendments (no)
Auxiliary request 2 - amendments (yes)
Admission of objection under Article 84 EPC into the appeal proceedings (no)
Auxiliary request 2 - sufficiency of disclosure (yes)
Admission of a document into the proceedings (yes)
Auxiliary request 2 - novelty and inventive step (yes)

Decisions cited:
G 0003/14

Catchword:

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Case Number: T 2277/14 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 April 2016

Appellant: (Opponent 2)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
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Appellant: (Opponent 3)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 October 2014 concerning maintenance of the European Patent No. 1644019 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: D. Boulois
I. Beckedorf

Summary of Facts and Submissions

I. European patent No. 1 644 019 based on application No. 04 753 925.9 was granted on the basis of a set of 30 claims.

II. Three oppositions were filed against the patent under Article 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step and covered a method of treatment, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The documents cited during the opposition proceedings included the following:
(1): AU54168/65
(3): WO03/072046
(12): Prescribing info for Adderal XR
(20): Popochin thesis, 1991
(21): Drug Metabolism and Disposition, 1994, Vol. 22, No 5, pages 770 to 775
(22): Int. J. of Pharmaceutics, 1995, 121, pages 157 to 167
(23): Biol. Chem. Hoppe-Seyler, 1992, Vol. 373, pages 375 to 380
(24): US 7659253
(25): US label for Vyvanse

IV. The present appeal by opponents 02 and 03 (hereinafter appellants 02 and 03) lies from the decision of the opposition division to maintain the patent as amended. The decision was based on 2 sets of claims filed with letters of 5 December 2013 as main request and of 11 August 2014 as auxiliary request.

The independent claims of the requests read as follows:

(a) Main request

"1. L-lysine-d-amphetamine.

2. L-lysine-d-amphetamine mesylate.

3. L-lysine-d-amphetamine hydrochloride.

4. A pharmaceutical composition in oral dosage form comprising a compound selected from:
L-lysine-d-amphetamine or a salt thereof;
L-lysine-d-amphetamine mesylate; and
L-lysine-d-amphetamine hydrochloride;
and one or more pharmaceutically acceptable additives.

19. Amphetamine in the form of L-lysine-d-amphetamine or a mesylate or hydrochloride salt thereof for use in decreasing abuse of amphetamines or salts thereof, in a subject in need thereof.

20. L-lysine-d-amphetamine or a mesylate or hydrochloride salt thereof for providing an amphetamine in a steady-state serum release curve without spiking blood serum concentrations, wherein said amphetamine is L-lysine-d-amphetamine or a mesylate or hydrochloride salt thereof and wherein said amphetamine maintains a steady-state serum release curve which provides therapeutically effective bioavailability of the amphetamine, but prevents spiking blood serum concentrations of the amphetamine when compared to the administration to the subject of the same amount of the amphetamine in the form of D-amphetamine."

(b) Auxiliary request

This request differed from the main request by the deletion of the term **"L-lysine-d-amphetamine hydrochloride"** in independent claim 4 and the deletion of dependent claim 14, resulting in a renumbering of all subsequent claims. Claims 18 and 19 of auxiliary request 1 thus correspond to claims 19 and 20 of the main request.

V. According to the decision under appeal, the subject-matter of claims 4 and 14 of the main request did not meet the requirements of Article 123(2) EPC. As regards claim 4, there was no disclosure in the application as filed of the oral administration of L-lysine-d-amphetamine. As regards claim 14, there was no disclosure in the application as filed for the treatment of children with the claimed compounds.

The opposition division did not admit any of documents (20)-(25), because they were filed late, namely two days before the oral proceedings, and *prima facie* not relevant.

The invention as claimed in the auxiliary request was sufficiently disclosed. The objections regarding specific terms used in the claims, such as *inter alia* "mesylate", "substantial euphoria", "a steady state serum release curve" or the objections raised against the pharmacokinetics parameters related to clarity and not to disclosure issues.

Claims 8-11, 13-15 and 30 were not considered as methods of treatment since they related to products as such.

As regards novelty, document (1) could not be prejudicial for novelty because it did not disclose directly and unambiguously L-lysine-d-amphetamine. As regards inventive step, document (3) was considered as the closest prior art, as far as the claimed priority was invalid, i.e for all claims except claim 3. This document related to the provision of an amphetamine composition for oral administration which eliminated spiking of drug levels, was resistant to abuse by parenteral routes of administration and had decreased bioavailability when taken at doses above the intended prescription. This document disclosed Glu-Glu-Amp, Ser-Amp and Phe-Amp but not L-lysine-Amphetamine. Example 27 and Table 46 of the contested patent allowed a direct comparison of the compounds of document (3) and the compound L-lysine-Amphetamine. The compound of the contested patent had a lower C_{max} but a higher AUC, thus demonstrating a reduced spiking (C_{max}) while maintaining a good bioavailability (AUC). The technical effect resulting from the difference provided an abuse-resistant form of amphetamine, while providing the same therapeutic benefit as amphetamine, and the objective problem was the provision of an administration form of amphetamine with improved abuse resistance. The skilled person would not have found a reasonable expectation of success in document (3), and the claimed subject-matter was found to be inventive.

As regards inventive step of claim 3, extended release formulations available at the priority date of the application were considered to represent the closest state of the art, such as Adderall XR® disclosed in document (12). Adderall XR® contained d/l amphetamine sulphate, d-amphetamine saccharate and d/l amphetamine aspartate monohydrate. The effect resulting from the difference was a reduced abuse-liability after

intranasal administration, and the objective problem was regarded as the provision of an administration form of d-amphetamine with reduced abuse-liability after intranasal administration. The opposition division saw in the compound of claim 3 a non-obvious alternative which could not be deduced from the prior art.

At the request of one of the opponents, the opposition division carried out also the problem-solution approach with document (1) as closest state of the art. This document disclosed D-Lysine-d-amphetamine, but not L-lysine-d-amphetamine, and the problem to be solved was seen as the provision of an alternative administration form of d-amphetamine.
As there was no incentive in document (1) to modify the disclosed compound, the opposition division concluded that the claims were inventive.

VI. With its statement setting out the grounds of appeal, appellant 02 resubmitted the pieces of evidence (20)-(25) and new evidence:
(27): US 7 659254

VII. With its statement setting out the grounds of appeal, appellant 03 made objections under Articles 84, 123(2), 100(b), 54 and 56 EPC.

VIII. With a letter dated 3 July 2015, the patent proprietor (hereinafter the respondent) requested that documents (20)-(25) and (27) filed by appellant 2 and the objection of lack of clarity raised by appellant 03 not be admitted into the proceedings.

IX. With a letter dated 8 July 2015, appellant 03 submitted new evidence:
(28): Declaration of Prof. Dr. Gmeiner

X. With a letter dated 2 March 2016, opponent 01 informed the board and the parties that it would not be attending the oral proceedings. Opponent 01 did not make any submission.

XI. In a communication dated 15 March 2016 sent in preparation of oral proceedings, the board gave its preliminary opinion. In particular, it stated that the request maintained by the opposition division, now the main request on file, did not meet the requirements of Article 123(2) EPC.

XII. With a letter dated 30 March 2016, the respondent filed auxiliary requests 1 to 3. Its main request remained the auxiliary request as maintained by the opposition division.

The subject-matter of the claims of auxiliary requests 1 and 2 differed from the main request as follows:

(a) Auxiliary request 1

The subject-matter of dependent claims 11 and 17 was deleted and the claims renumbered accordingly. Independent claims 16 and 17 thus corresponded to independent claims 18 and 19 of the main request.

(b) Auxiliary request 2

The subject-matter of claims 1-17 was identical to that of claims 1-17 of auxiliary request 1 except for the deletion in independent claim 4 shown in bold:

4. A pharmaceutical composition in oral dosage form comprising a compound selected from:

L-lysine-d-amphetamine ~~**or a salt thereof**~~;
L-lysine-d-amphetamine mesylate; and
L-lysine-d-amphetamine hydrochloride;
and one or more pharmaceutically acceptable additives.

XIII. Oral proceedings took place on 14 April 2016.

XIV. The arguments of the appellants as far as relevant for the present decision may be summarised as follows:

Main request - Amendments

According to appellant 02, the application as filed could not provide a basis for independent claims 2, 4, 11, 17, 18 or 19 of the main request.
The disclosure of L-lysine-d-amphetamine mesylate (hereinafter Lys-amp) was an error and could not form part of the application as filed since the doses given in the only passage of the original application WO2005/000334 disclosing Lys-amp mesylate, namely paragraphs [0082]-[0085], corresponded to the di-mesylate salt, while said paragraphs and corresponding figures 52A-55A-B related to the mesylate salt.
There was no basis in the original application for the feature "L-lysine-d-amphetamine or a salt thereof" in claim 4. In particular, the subject-matter of claim 39 referred to other claims for which a selection had to be made for the amphetamine, the amino acid, and between a salt and an ester.
There was also no basis for the use of "L-lysine-d-amphetamine hydrochloride" in claims 18 and 19 of the main request.
The dosage of claim 11 was an isolated feature of paragraph [0236] which could not be generalised.

A "once daily" administration in claim 17 constituted also a selection of several possibilities and was an unallowable intermediate generalisation.
The subject-matter of claim 18 related to a selection of specific compounds in a general use not disclosed for such specific compounds.

According to appellant 03, there was no direct and unambiguous disclosure whether explicit or implicit, of the combination of features of claim 4, namely of a composition with additives.
A composition as such was not disclosed originally, and Lys-amp was originally not the preferred compound. Thus various selections had to be performed to arrive at the specific claimed combination of claim 4.
There was also no direct and unambiguous disclosure in the original application of the term "or a salt thereof" in claim 4, and thus of the presence of any salt in the claimed composition. A multiple selection was again necessary to derive the claimed salt.
The subject-matter of dependent claims 5 to 11 was also not disclosed in combination with the features of claim 4.
The dosage of claim 11 and the "once daily administration" of claim 17 were also not derivable from the original application. There was also no basis for the treatment of an "adult" in claim 13.

Main request - Sufficiency of disclosure

According to appellant 02, the subject-matter of claims 5, 7, 8 and 19 was not sufficiently disclosed. In order to establish the pharmacokinetic properties of these claims, it would have been necessary to carry out extensive in vivo tests in patients, which was considered an unacceptable and undue burden. The patent

also did not provide objective definitions and criteria for determining the meaning and scope of some claimed terms, namely "substantial euphoria", "euphoria", "AUC", "amphetamine", "spiking", and "increased blood serum concentrations". Moreover, the use of claim 18, namely decreased amphetamine abuse, was not substantiated by the patent, since Lys-amp did not achieve such a decrease.

According to appellant 03, the subject-matter of claims 2, 5-11 was not sufficiently disclosed in the description. There was no disclosure of a composition in an oral dosage form according to claim 4, or of any effect achieved by such composition, especially in the examples. Moreover, the subject-matter of claims 5, 7 and 8 was defined by a result to be achieved, without mentioning the technical means necessary to achieve it. There were also no data concerning the treatment of ADHD, narcolepsy or ADD which were mentioned in claims 12, 14 and 16.

Auxiliary request 1

The same arguments and objections applied to this request.

Admission of document (28) into the proceedings

Appellant 03 argued that document (28) could not have been filed before the opposition division. Some time had been needed to produce the experimental data, which had thus been filed as early as possible in the appeal proceedings.

Auxiliary request 2 - Clarity

The wording of claim 4 was objected to by appellant 03, since its subject-matter included the term "L-lysine-d-amphetamine or a salt thereof" as well as the alternative of "L-lysine-d-amphetamine mesylate". The scope of claim 4 was seen as unclear, as it was ambiguous what was encompassed by the list defining the compound, namely whether the claim should encompass compositions comprising any salt of Lys-amp, or should be limited to only Lys-amp and its mesylate salt, or any salt together with the mesylate salt.

Auxiliary request 2 - Novelty

According to appellant 02, page 7 and example 24 of document (1) were novelty-destroying. Appellant 03 also considered the same passages of document (1), to provide an explicit and implicit disclosure respectively of the claimed subject-matter.

Document (1) disclosed on pages 2 and 4 the amphetamine derivatives of general formula I and IV, in which the moiety X or A was a member selected from the group consisting of α-amino carboxylic acids, wherein lysine was disclosed in a list on page 4. The description mentioned on page 7 that acids of the L-series were preferred. Therefore, α-amino carboxylic acids in the L-configuration were specifically mentioned as the preferred embodiment in document (1). The description specified on pages 7 and 8 that the use of D(+)-amphetamine was preferred. Thus, there was an explicit disclosure of Lys-amp, in view of the formula I or IV, in combination with the possibilities given in pages 4 or 7 for the moiety conjugated to amphetamine.

Document (1) mentioned also that the protecting acyl group used for the purpose of synthesis might be

removed by conventional means, leading directly and unambiguously to conjugates of amphetamine and L-α-amino carboxylic acids.

Example 24 disclosed the conjugate N-tosyl-L-lysine-d-amphetamine, and stated in the description on page 14 how to remove the protective tosyl group. Thus the claimed Lys-amp was implicitly disclosed in this example.

Compositions comprising the conjugates of document (1) were also disclosed in the description on page 17 and in the examples.

Auxiliary request 2 - Inventive step

According to appellant 02, document (1) was the closest prior art, since the desired abuse resistance was not achieved in document (3). Document (1) showed amphetamine conjugates, from which it was easy to extract d-amphetamine. Thus, the potential of abuse was inherent for the conjugates of document (1), in the same way as for the products of document (3). Document (12) did not relate to a prodrug and was not appropriate as closest prior art.

Document (1) taught that the protective groups could be cleaved, and clearly taught the synthesis of protected Lys-amp from the disclosure of example 24. Moreover, this document mentioned all possible salts for the conjugate. Appellant 02 considered that any advantage that might be acknowledged had to be seen as a bonus effect, and there was no meaningful reduction in abuse potential, since it was always possible to increase the dose of the conjugate to reach the abuse effects.

The problem over document (1) was seen as the provision of an alternative conjugate or composition. Document (1) taught the solution on page 14, namely to make a de-tosylation.

According to appellant 03, document (3) was the closest prior art, but document(1) could be seen as an alternative. The difference between the claimed subject-matter and the disclosure of document (3) was the amino acid, thus L-lysine. The opposed patent found that with the provision of Lys-amp, peak plasma levels of amphetamine could be reduced, while the bioavailability of amphetamine remained substantially the same after oral administration. The technical problem allegedly solved by the opposed patent was thus the provision of an amphetamine conjugate for achieving said effects. Document (3) gave a pointer to use L-lysine for covalent attachment to amphetamine, since it mentioned that the amino acids to be used had to be L-amino acids in paragraph [0057]. Example 7 provided a pointer towards the use of single amino acids, since this example of document (3) showed a reduction of C_{max} with some conjugates of amphetamine and amino acid. Moreover, using an amino acid with a positively charged chain could have been expected to improve the pharmacokinetic parameters of the conjugate. The skilled person would have therefore tried other amino acids, and inevitably would have selected lysine, which was only one possibility among twenty different possible amino acids. Figure 43 of the patent showed evidence that the skilled person would have chosen lysine.

Document (1) represented the closest prior art with respect to claim 3, in view of the partial priority invalidity. This document disclosed the possibility of

making hydrochloride salts and shared all the claimed technical features, and this made the provision of an hydrochloride salt of Lys-amp obvious.

XV. The arguments of the respondent, as far as relevant for the present decision, may be summarised as follows:

Main request - Amendments

The subject-matter of claim 2 of the main request did not infringe Article 123(2) EPC in view of the explicit basis found in paragraphs [0081]-[0085]. The doses disclosed in the same paragraphs related explicitly to the mesylate salt of Lys-Amp which, in view of the structure of lysine, could only be a dimesylate. The mesylate salt of Lys-amp did comprise two mesylates, and the common denomination for this conjugate was simply Lys-Amp mesylate. Moreover, Figure 2 showed that the hydrochloride salt was in fact also a di-hydrochloride salt.

The subject-matter of claim 4 was also derivable from original claims 11, 14 and especially claim 39 wherein a salt of the composition of claims 10-38 was disclosed. Since the patent related to oral administration, it was obvious that the now claimed conjugate could only be in the form of a salt and that the preferred conjugate was Lys-amp. Thus all general statements of the original application applied to the preferred Lys-amp.

The subject-matter of claim 11 was disclosed in original example 33 at paragraph [0236], and the subject-matter of claim 17 in paragraph [0142] of the original application. The same dosage could be found in Table 50.

The objection against claim 13 was a new objection raised for the first time during oral proceedings. It was clear from the original application that the treatment of ADHD was the main purpose of the invention.

A basis for claim 17 could be found in paragraphs [0140] and [0142].

Main request - Sufficiency of disclosure

The objections raised against the results to be achieved of claims 5, 7 and 8 related to lack of clarity rather than to sufficiency, as did the objections to the terms "euphoria", "substantial euphoria", "AUC", "amphetamine" and "spiking" in claims 5, 7, 8 and 19. All said objections were however spurious and unsupported by any evidence.
As to the objections against the claimed diseases, there could be no doubts, since these treatments were well known for amphetamine.

Auxiliary request 1

All the arguments put forward for the objections raised against the main request applied for this request.

Admission of document (28) into the proceedings

Document (28) could have been filed earlier, and certainly should not have been filed after the statement of grounds of appeal. Its content was not relevant for the case, since there was no disclosure in document (1) that the compounds of the example had to be de-tosylated.

Auxiliary request 2 - Clarity

The clarity objections had been raised for the first time in appeal proceedings, and could have been raised during the opposition proceedings. Claim 4 of the main request patent was essentially identical to claim 6 of the granted patent, which depended on claims 1 and 3. The only difference between claim 4 of the patent maintained by the opposition division was that the subject-matter of claims 1 and 3 was now set out explicitly. This claim was therefore not open for a re-examination for clarity (see decision G 3/14).

Auxiliary request 2 - Novelty

Document (1) did not disclose directly and unambiguously Lys-amp or any of its salts. The product of example 24 was a final product, as confirmed by several parts of the description of document (1), and the disclosure on pages 4 or 7 necessitated a selection among several lists of possibilities. As to the possibility of detosylation of the product of example 24, there was no disclosure or instructions that it inevitably had to apply to the conjugate of example 24.

Auxiliary request 2 - Inventive step

Document (3) was the closest prior art to the subject-matter not entitled to the first priority. In any case, document (3) was more relevant than document (1), which was in no way directed to any use similar to that of the patent. In contrast, document (3) was directed to the prevention of abuse of amphetamine.

Starting from document (3), it was clear from the test results of example 7 of document (3) that the conjugates disclosed therein would not solve the problem of providing an abuse-resistant form of amphetamine, since the C_{max} of the conjugates remained high, while the AUC decreased significantly. The conjugate claimed by the opposed patent showed the exact opposite. The skilled person would not have tried to modify the conjugate disclosed in document (3) to arrive at the claimed subject-matter in view of these results, but also in view of the fact that lysine was not suggested explicitly in this document. Moreover, the amino acids used in example 7 of document (3) were Glu, Ser and Phe and had different properties from Lys.

Document (1) could not be the closest prior art in respect of the subject-matter entitled to the first priority, but it was rather document (12). The problem raised by document (1) was the diminution of the analeptic effect of the conjugate, which was the contrary of the opposed patent, and the skilled person would not have seen any incentive to change the disclosed conjugates to arrive at the claimed subject-matter.

XVI. **Requests**

The final requests of the parties were:
Appellants 02 and 03 requested that the decision under appeal be set aside and that European patent No. 1 644 019 be revoked.

The respondent requested that the appeals be dismissed or, in the alternative, that in setting aside the decision under appeal the patent be maintained in

amended form on the basis of any of auxiliary requests 1 to 3 filed with letter of 30 March 2016.

Reasons for the Decision

1. Main request - Sufficiency of disclosure

The subject-matter of claims 2, 4-11, in particular of claims 5, 7 and 8, as well as he subject-matter of claims 12, 14, 16, 18 and 19 was objected for insufficient disclosure. Certain terms of these claims, namely "*substantial euphoria*", "*AUC*", "*amphetamine*", "*spiking*", "*increased blood concentration*" were furthermore specifically objected.

1.1 Claim 2

The subject-matter of claim 2 relates to a specific compound, i.e. the mesylate salt of Lys-amp.

Example 2 or Figure 2 of the specification EP 1 644 019 B1 explicitly shows the synthesis of Lys-amp and its hydrochloride salt through treatment of a protected Lys-amp conjugate by hydrochloric acid, and is thus a direct disclosure of the conjugate of claim 1 and of its hydrochloride salt of claim 3 of the main request. Starting from the teaching of example 2 and Figure 2, the skilled person would not see any difficulty in obtaining any alternative salt of Lys-amp, since that belongs to routine activity.

The skilled person therefore finds sufficient teaching in the patent specification on how to prepare the mesylate salt of Lys-amp.

1.2 Claims 4, 6, 9, 10, 11

The subject-matter of these claims relates to pharmaceutical compositions in oral dosage forms comprising specific compounds, possibly present in specific amounts, for the preparation of which the skilled person would not see any difficulty. Moreover, instructions for making various oral dosage forms are to be found in paragraphs [0107] to [0124] of the specification EP 1 644 019 B1.

1.3 Claims 5, 7, 8

These claims include respectively the following features: "*wherein said compound provides a therapeutically effective amount of amphetamine without providing substantial euphoria*", "*wherein said compound is present in an amount sufficient to provide a therapeutically bioequivalent area under the curve (AUC) of amphetamine when compared to amphetamine alone, but in an amount insufficient to provide a* C_{max} *which results in euphoria*" and "*wherein said compound is present in an amount sufficient to maintain a steady-state serum release curve of amphetamine which provides a therapeutically effective bioavailability of amphetamine but prevents spiking or increased blood serum concentrations as occurs with amphetamine alone*".

The description provides ample and sufficient teaching as to the pharmacokinetics of the claimed compounds or composition comprising them, and shows in particular that all claimed effects are intrinsically achieved by the claimed compounds as such, without needing further technical means, that is Lys-amp and its specific mesylate or hydrochloride salts. It explains that a

reduction in the euphoric effect is linked with the pharmacokinetic properties of said compounds, in particular a decreased C_{max} (see par. [0027] of the specification EP 1 644 019 B1), and shows that such decrease of C_{max}, as well as the prevention of "*spiking*" or "*increased blood serum concentration*", is indeed obtained by the claimed compounds as such, while said compounds still provide a therapeutically bioequivalent area under the curve (AUC) of amphetamine when compared to amphetamine administered alone (see for instance Tables 3 and 46).

As to the objections relating to the terms "*substantial euphoria*", "*AUC*", "*amphetamine*", "*spiking*", "*increased blood concentration*", they relate to clarity issues and not to sufficiency of disclosure. Since the terms were present in the granted claims in the same context, according to G 03/14 they are not open for re-examination under Article 84 EPC in the present opposition proceedings.

1.4 Claims 12, 14, 16

The subject-matter of claims 12 and 16 relates to the treatment of ADHD and ADD by the conjugates. Amphetamine is well known for the treatment of ADHD and ADD (see for instance document (3) or description of the contested patent, *inter alia* par. [0005],[0008] and [0009]). Since the patent description shows that the claimed conjugates dissociate and release amphetamine in the plasma (see for instance Table 1), there cannot be any doubt for the skilled person that the claimed conjugates are also able to treat the same diseases as amphetamine. This objection is thus unfounded.

The subject-matter of claim 14, directed to the treatment of narcolepsy by the claimed conjugates, was objected to for the first time during oral proceedings. An objection for insufficient disclosure for the treatment of narcolepsy is however also unfounded. Amphetamine and its derivatives are well known for the treatment of narcolepsy, as highlighted in the description of the contested patent (see for instance specification par. [0004]), and the patent description shows that the claimed conjugates dissociate and release amphetamine in the plasma (see Table 1). There is thus no reason to doubt that the claimed conjugates have an effect on narcolepsy, and there is also sufficient disclosure as regards this claimed subject-matter.

1.5 Claim 18

The subject-matter of claim 18 relates to Lys-amp or its mesylate salt for use in reducing amphetamine abuse. As regards reducing this undesirable side effect, the description of the contested patent gives ample teaching about how the claimed conjugates are able to reduce the potential abuse of amphetamine when administered nasally or parenterally. It explains *inter alia* that the conjugates are prodrugs which are converted into their active form in the blood by normal metabolic processes. Hence, covalent attachment of a chemical moiety to amphetamine decreases its pharmacological activity when administered by injection or intranasally (see for instance par. [0016]-[0019] of the specification). This property is indeed proven in numerous examples of the patent (see for instance examples 14 and 15). There is thus no reason to doubt the sufficiency of disclosure as

regards the reduction in amphetamine abuse linked with the claimed conjugates.

1.6 Claim 19

The subject-matter of this claim relates to Lys-amp or its mesylate or hydrochloride salt suitable "*for providing an amphetamine in a steady-state serum release curve without spiking blood serum concentrations*" and for maintaining "*a steady-state serum release curve which provides therapeutically effective bioavailability of the amphetamine, but prevents spiking blood serum concentrations of the amphetamine when compared to the administration to the subject of the same amount of the amphetamine in the form of D-amphetamine*".
As mentioned above for the subject-matter of dependent claims 5, 7 and 8, the description of the contested patent provides sufficient teaching as to the pharmacokinetics of the claimed compounds, especially regarding the serum release, the absence of spiking and the release of amphetamine in the plasma (see for instance Tables 3 and 46 and par. [0027]) or [0098] of the specification). There is sufficient disclosure as regards this claimed subject-matter.

1.7 The claimed invention is therefore sufficiently disclosed.

2. Main request - Amendments

The subject-matter of claims 2, 4, 11, 13, 17, 18 and 19 has been objected to by the appellants on the ground that it extends beyond the application as originally filed.

2.1 Claim 2

2.1.1 The subject-matter of this claim refers to the specific compound "*L-lysine-d-amphetamine mesylate*" for which a literal disclosure is to be found in paragraphs [0082]-[0085] of the application as originally filed, namely publication WO2005/000334. These passages are references to a specific embodiment of the invention shown in figures 52A-B, 53A-B, 54A-B and 55A-B and disclosing the d-amphetamine plasma levels after oral administration of Lys-amp mesylate. There is thus a direct and unambiguous disclosure of the compound Lys-amp mesylate in the application as originally filed and the subject-matter of this claim does not infringe Article 123(2) EPC.

2.1.2 The board could not follow the arguments of appellant 02 that the skilled reader would consider the reference to "L-lysine-d-amphetamine mesylate" in paragraphs [0082]-[0085] to be an error and that said skilled reader would not consider that substance to be disclosed by the application as filed. This argumentation was based on the fact that the oral doses of L-lysine-d-amphetamine disclosed in said paragraphs [0082]-[0085] corresponded in fact to oral doses of the dimesylate salt. This argument could however not be followed in view of the explanations of the respondent that the term "*L-lysine-d-amphetamine mesylate*" related to the dimesylate salt, and that both terms were synonyms. This explanation makes sense and appears sound in view of the chemical structure of Lys-amp, which contains two free amino groups carried by the amphetamine.

2.2 Claim 4

The objections against claim 4 relate to:
- the combination of features relating to an "*oral dosage form*" and "*one or more pharmaceutical additives*",
- the combination of "*L-lysine-d-amphetamine or a salt thereof*" with "*L-lysine-d-amphetamine mesylate*",
- the presence in the claim of the term "*or a salt thereof*" relating to Lys-amp.

2.2.1 Concerning the combination of "*oral dosage form*" and "*one or more pharmaceutical additives*", it is clear from the application as originally filed that the object of the invention is an oral dosage form which can be in the form of a tablet, capsule, oral solution or oral suspension (see par. [0161] or original claim 11). It is also clear from the description of the application as originally filed that these compositions may comprise excipients or additives, as explicitly mentioned for instance in paragraphs [0123] or [0137] or any of paragraphs [0121]-[0136]). As the choice of the oral dosage form and the presence of additives does not constitute any selection, this part of claim 4 is derivable directly and unambiguously from the application as originally filed.

Furthermore, the combination of these features with the claimed specific compounds, namely Lys-amp, Lys-amp mesylate and Lys-amp hydrochloride constitutes a selection in an unique list, since the claimed compounds are among the preferred compounds disclosed in the figures and examples of the original application. This part of claim 4 is thus also derivable directly and unambiguously from the application as originally filed.

2.2.2 As regards possible originally undisclosed combinations of "*L-lysine-d-amphetamine or a salt thereof*" with "*L-lysine-d-amphetamine mesylate*", the wording of claim 4 makes clear that its subject-matter relates to a composition wherein a unique compound is selected from three possibilities, namely "*L-lysine-d-amphetamine or a salt thereof*" and "*L-lysine-d-amphetamine mesylate*", excluding the possibility of a combination of different variants of L-lysine-d-amphetamine. Indeed, in the presence of the terms "*a compound*" in combination with "*selected from*", the skilled reader would not interpret the subject-matter of claim 4 as potentially comprising a mixture of several alternative active compounds, namely a mixture of "*L-lysine-d-amphetamine*" or "*a salt thereof*" and the "*mesylate*". This part of claim 4 is thus derivable directly and unambiguously from the application as originally filed.

2.2.3 With reference to the term "*a salt thereof*", salts are mentioned in the application as originally filed exclusively in claim 6, claim 39 and paragraph [0168], as follows:
- "*a compound comprising amphetamine or salts thereof covalently attached to a single amino acid*" in original claim 6,
- "*an ester or salt of the composition of claims 10-38*" in original claim 39, wherein claim 10 refers to "*a composition comprising amphetamine and a chemical moiety covalently bound to said amphetamine*",
- "*the toxicity of the compound may be lower than that of the amphetamine when amphetamine is delivered in its unbound state or as a salt thereof*" in the original description in paragraph [0168].

The application as originally filed dealt very generally with an "*amphetamine and a chemical moiety*

covalently bound to said amphetamine" (see for instance original claim 10). The term "*amphetamine*" refers however in the original description and claims not to the specific chemical "*amphetamine*" but more generally to a whole family of compounds consisting of several possibilities. Original claims 9 and 28 mention in particular that "*the amphetamine is selected from amphetamine, methamphetamine, methylphenidate, or mixtures thereof*". This is confirmed by the description, which discloses in paragraph [0095] that "*amphetamine"* means "*any of the sympathomimetic phenethylamine derivatives which have central nervous system stimulant activity, such as but not limited to, amphetamine, methamphetamine, p-methoxyamphetamine, methylenedioxyamphetamine, 2, 5-dimethoxy-4-methylamphetamine, 2,4, 5-trimethoxyamphetamine and 3,4-methylenedioxymethamphetamine*".

The chemical moiety bound to the amphetamine can also be selected from several possibilities, such as an amino acid, a dipeptide or a tripeptide (cf. par. [0018] and original claim 2). The single amino acid can in particular be lysine, as claimed in dependent claims 7, 8 or 14 without specifying whether it relates to the (L) or (D) isomer. The description mentions that the term "*single amino acid*" in the original application refers to a list of numerous multiple possibilities selected from naturally occurring (L-) or (D) amino acids, and L-lysine and D-lysine are explicitly mentioned (see par. [0101], and in particular par. [0108]).

The specific compounds claimed in claim 4 of this request, namely Lys-amp and Lys-amp mesylate, were selected preferred compounds of the original application, and are disclosed as such in the original

application only in the figures and in the examples. Hence, a reference to "*a salt*" in general of the specific compound Lys-amp is to be found nowhere in the original application, and cannot be extrapolated from its disclosure in original claims 6, 39 and par. [0168] without making multiple selections.

The term "*and a salt thereof*" in claim 4 is thus not derivable directly and unambiguously from the application as originally filed, and for this reason the main request does not meet the requirements of Article 123(2) EPC.

2.3 Claims 5-10

The subject-matter of these claims was objected to in view of its combination with the subject-matter of claim 4. Since claims 5-10 refer to claim 4, they raise the same problem under Article 123(2) EPC in relation with the feature "and a salt thereof".
As to the remaining subject-matter of these claims, it does all relate to a further selection of features, since they all relate to general features applied to the compositions of the contested patent.
A basis was found as follows:
- claims 5, 6 and 7 find a basis *inter alia* in original claims 55, 29 and 42 respectively,
- claims 8, 9 and 10 are disclosed respectively and *inter alia* in paragraphs [0029, [0119] and [0140] of the original application.

2.4 Claim 11

The subject-matter of this dependent claim relates to a specific amount of the active compound in the composition of independent claim 4, namely Lys-amp or a

salt thereof and the mesylate salt thereof, and states that "*said compound is present in an amount of 25 or 75 mg for oral administration*".

This amount is first disclosed in paragraphs [082] to [085] of the original application, which refer to Figures 52A-B, 53A-B, 54A-B and 55A-B, relating to the oral administration of 25 mg and 75 mg of the specific compound Lys-amp mesylate. This disclosure is thus not made for Lys-amp as such or another salt thereof.

The same amounts are further disclosed in example 33 of the original application wherein it is mentioned that "*L-lysine-d-amphetamine was orally administered at doses approximating the lower (25 mg) and higher (75 mg) end of the therapeutic range based on d-amphetamine base content of the doses*". Example 33 relates however to the specific treatment of ADHD and does not disclose a composition with 75 mg of the active agent but only the use of 3 capsules of 25 mg thereof, and the doses disclosed therein cannot be generalised to any treatment involving Lys-amp. Moreover, this example does not refer to salts of Lys-amp.

The subject-matter of dependent claim 11 is thus not derivable from the original application, since at least a part of it corresponds to specific embodiments which cannot be generalised. For this reason the main request does not meet the requirements of Article 123(2) EPC.

2.5 Claim 13

The subject-matter of this claim is dependent on claim 12 relating to the treatment of ADHD and was objected to for the first time during oral proceedings under

Article 123(2) EPC. Claim 13 further specifies that the type of subject to be treated "*is an adult*".

It is evident from the application as originally filed that the treatment of ADHD is one of the main therapeutic applications the invention aims to treat, as shown in paragraphs [0003]-[0009], [0169] or in example 33. The description mentions in general the treatment of humans adults by the compounds of the present invention and the corresponding necessary dose range (see par. [0140]). The treatment of ADHD is thus transposable to adults from the passages cited, and the subject-matter of this claim is derivable directly and unambiguously from the application as originally filed.

2.6 Claim 17

The subject-matter of this claim depends on claims 12 to 16, referring to the treatment of ADHD, narcolepsy, obesity and ADD by any compound of claims 1-3, namely Lys-amp and its mesylate or hydrochloride salt, and specifies that "*the compound is for administration once daily*".

The description as originally filed disclosed in paragraph [0142] that "c*ompositions of the invention may be administered in a partial, i.e., fractional dose, one or more times during a 24 hour period, a single dose during a 24 hour period of time, a double dose during a 24 hour period of time, or more than a double dose during a 24 hour period of time. Fractional, double or other multiple doses may be taken simultaneously or at different times during the 24 hour period*".

The combination of a mode of administration selected from several alternatives with three of the preferred compounds of the examples and the figures is not derivable directly and unambiguously from the application as originally filed, and for this reason claim 17 of the main request does not meet the requirements of Article 123(2) EPC.

2.7 Claim 18

The subject-matter of this claim is directly and unambiguously disclosed in claim 56 as originally filed.

2.8 Claim 19

The subject-matter of this claim derives from the combination of a selection of three preferred compounds of the invention, namely Lys-amp and its hydrochloride or mesylate salts, with a general property attributed to the compounds of the contested patent "*for providing an amphetamine in a steady-state serum release without spiking blood serum concentrations, wherein said amphetamine is L-lysine-d-amphetamine or a mesylate or hydrochloride salt thereof and wherein said amphetamine maintains a steady-state serum release curve which provides therapeutically effective bioavailability of the amphetamine, but prevents spiking blood serum concentrations of the amphetamine when compared to the administration to the subject of the same amount of the amphetamine in the form of D-amphetamine*", which is to be found *verbatim* in paragraphs [0115], [0117] and [0151] of the original application. The subject-matter of this claim is thus derivable directly and unambiguously from the original application.

2.9 Accordingly, the subject-matter of claims 4, 11 and 17 goes beyond the content of the application as originally filed, and the main request does not meet the requirements of Article 123(2) EPC for this reason.

3. Auxiliary request 1 - Amendments

Since the term "or a salt thereof" is still present in claim 4 of auxiliary request 1, this request does not meet the requirements of Article 123(2) EPC (cf. points 2.2 and 2.9 above).

4. Auxiliary request 2 - Amendments

The subject-matter of claims 1-17 of auxiliary request 2 corresponds to the subject-matter of claims 1-10 12-16, 18-19 of the main request, with the deletion of the term "*or a salt thereof*" in claim 4. This request therefore meets the requirements of Article 123(2) EPC.

5. Auxiliary request 2 - Sufficiency of disclosure

The subject-matter of claims 1-17 of auxiliary request 2 corresponds to that of the main request with some deletions. As the main request was sufficiently disclosed, this conclusion applies *mutatis mutandis* to this request.

6. Admission of document (28) into the proceedings

Document (28) was filed by the appellant at a late stage in the appeal proceedings and deals with certain aspects of common general knowledge of the technical field of the contested patent, in particular about the chemical reaction of de-tosylation. It does not provide new information and may serve to illustrate the common

general knowledge and arguments relating to novelty and inventive step brought into the proceedings. Consequently, document (28) is admitted into the proceedings (Article 13(1) RPBA).

7. Auxiliary request 2 - Admission of the ground of Article 84 EPC into the proceedings

A clarity objection against claim 4 has been raised for the first time in the proceedings by appellant 03 in its statement of grounds of appeal. This objection had not been raised before the opposition division.

The board agrees that a discussion with respect to Article 84 EPC must definitively address any newly drafted claims. This is however not the case with the subject-matter of claim 4 objected to by appellant 03, which was already on file as such before the opposition division, and which was decided upon in the appealed decision. Moreover, the subject-matter of claim 4 obviously results from the combination of the subject-matter of claims 1-4 and 6 as granted and it appears immediately and *prima facie* that this claim as such cannot be open to a re-examination under Article 84 EPC (cf. decision G 3/14).

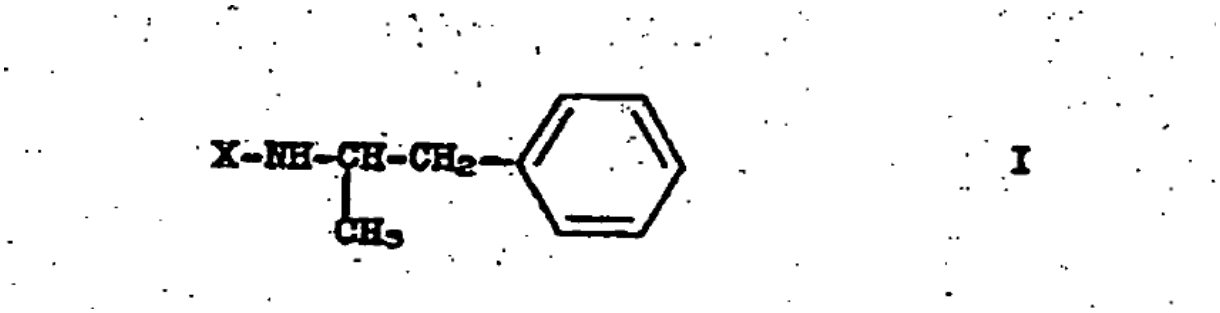
For these reasons, the board decides not to admit this objection into the appeal proceedings (Article 12(4) RPBA)

8. Auxiliary request 2 - Novelty

8.1 Document (1) was mentioned as relevant for the novelty of the claimed subject-matter, in particular in view of its disclosure on page 7 and in example 24, which were respectively considered to be an explicit and an

implicit disclosure of the claimed conjugate L-Lysine-d-amphetamine. The general Formula IV on page 4 was also considered.

8.1.1 Document (1) relates to products of the following formula I:



I

wherein X is an acyl group of an optically active alpha-amino acid having a free or protected alpha-amino group (see document (1), page 2).

In all parts of the description of document (1) it is however constantly necessary to make a selection from multiple lists, namely among a list of amino acids and their specific L-or D- forms and among a list constituted by isomers and racemate of amphetamine.

The description of document (1) specifies in particular on page 7 that the product may be "*a compound of formula I above having a free alpha-amino group*", wherein the "*optically active alpha-amino carboxylics can belong to the D- or L-series*" of a list of 18 amino acids, including lysine. It specifies in the same paragraph that "*acids of the L-series are preferred*", even if it appears from the examples that the D- amino acids may also be used, as shown by the conjugate of example 23 which contains D-lysine (see page 7, lines 5-21).

As regards amphetamine, the description on page 7 further mentions that "*amphetamine in all its stereochemical forms, including its racemate can be employed*" but *"the use of optically pure D(+)-amphetamine, i.e. the (+) rotary form of phenyl-2-aminopropane configuratively derived from D-phenylalanine is preferred*" (see page 7, lines 22 to page 8, line 3). The possible use of the racemate or of the D- form is also mentioned on page 6 (see last par.).

Thus, the description on page 7 not only does not disclose directly and unambiguously a conjugate made from L-lysine and D(+)-amphetamine, but also discloses several possible alternatives for the amino acid and for amphetamine, for which a multiple selection would have to be made to arrive at the compound claimed in claim 1 of the main request, namely Lys-amp.

It is in particular not possible to see in the disclosure on page 7 a combination of the preferred D(+)-amphetamine with an amino acid selected from a unique list, as argued by the appellants, since the racemate or the other isomer of amphetamine are explicitly mentioned in the same passage, and indeed used in example 6 of document (1). In any case, it would have been necessary to take into account also the preferred alternatives for the X radical of Formula I disclosed on pages 5 and 6 of document (1) from which L-lysine is absent despite the mention of numerous alternative L- amino acids.

Consequently, the disclosure of formula I and of the description on page 7 does not directly and unambiguously disclose Lys-amp.

8.1.2 Example 24 discloses the preparation of N-tosyl-L-lysine-D(+)-l-phenyl-propyl-(2)-amide, thus N-tosyl-L-lysine-d-amphetamine. The description of document (1) teaches further on page 14 that "*any of the group which protects the alpha-amino function...may be cleaved*" and that "*a tosyl group can be removed by the treatment of a so-substituted amide of formula I above with sodium in liquid ammonia*" (see page 14, second par.).

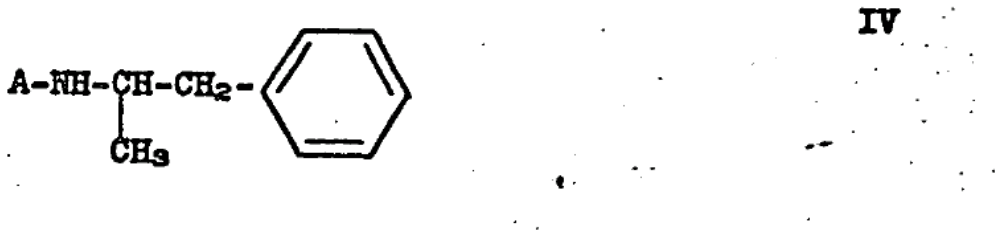
It is however clear that the compound tosyl-L-lysine-d-amphetamine disclosed in example 24 is a final product and not an intermediate product which should inevitably be detosylated. The N-tosyl-L-lysine moiety is indeed presented in the description as one of the preferred alternative acyl moieties to be conjugated with amphetamine (see page 5, last par. to page 6, 1st par.). It is furthermore clear from the formulation examples 28-30 of document (1) that the N-protected conjugates are directly incorporated into tablets or capsule and are not seen as intermediate products.

In any case, the content of a prior-art document cannot be treated as a reservoir from which features or parts of the description pertaining to separate embodiments can be combined in order to create artificially a particular embodiment which would destroy novelty, unless the document itself suggests directly and unambiguously such a combination of features.

In the present case, though the description of document (1) makes clear that it is possible to de-protect the alpha-amino acid function, it is not possible to deduce from this disclosure that the compound synthesised in example 24 is inevitably de-tosylated.

Consequently, the disclosure of example 24 does not directly and unambiguously disclose Lys-amp.

8.1.3 Formula IV of document (1) was also mentioned as a potentially novelty-destroying disclosure. Formula IV reads as follows:



wherein A is selected from an acyl moiety of an optically active alpha-amino group having a free or protected alpha amino group (see page 4, first par. - page 5, first par.). The corresponding text to Formula 4 on page 4 gives several possibilities for the acyl moiety, such as an amino acid or an acyl protected amino acid. Lysine is mentioned as a potential acyl moiety, without disclosing whether it relates to the L- or D- isomer. Said passage does not give any information as to the isomeric form of amphetamine associated thereto. This formula and the passage do not directly and unambiguously disclose Lys-amp either.

8.2 The subject-matter of independent claims 1-4, 16 and 17 of auxiliary request 2 is new, and this request meets the requirements of Article 54 EPC.

9. Auxiliary request 2 - Inventive step

9.1 The invention relates to conjugate compounds comprised of amphetamine covalently bound to a chemical moiety in a manner that diminishes or eliminates pharmacological activity of amphetamine until released after oral administration (see patent specification par. [0001]-

[0002]). Amphetamine is prescribed for the treatment of various disorders, including attention deficit hyperactivity disorder (ADHD), obesity and narcolepsy, and for its stimulation effect on the central nervous system. Because of its stimulating effects, amphetamine is often abused.
The invention is thus directed to an anti-abuse/ sustained-release formulation which maintains its therapeutic effectiveness and its therapeutically effective blood concentrations following oral administration, and which provides a therapeutically bio-equivalent activity when compared to amphetamine taken only orally (see patent specification par. [0003], [0004], [0021], [0022] or [0027])). The invention further relates to formulations which diminish or reduce the euphoric effect, by releasing amphetamine gradually over an extended period of time, thereby eliminating spiking of drug levels or high drug C_{max} linked with the euphoric effect.
The compositions or conjugates are also resistant to abuse by parenteral routes of administration, such as intravenous "shooting", intranasal "snorting", or inhalation "smoking", that are often employed in illicit use. Treatment of ADHD or ADD, obesity and narcolepsy with compositions of the invention results in substantially decreased abuse as compared to existing stimulant treatments (see patent specification par. [0001]-[0004]).

9.2 Document (1) was considered as the closest prior art by appellants 02 and 03, while document (3) was considered as closest prior art by appellant 03 and by the respondent, and was also the choice of the opposition division in its decision. The opposition division also mentioned document (12) as closest state of the art for the subject-matter of claim 3.

9.2.1 Document (12) relates to the commercial product Adderall XR® which contains sustained-release forms of d/l amphetamine sulphate, d-amphetamine saccharate and d/l amphetamine aspartate monohydrate. This document therefore does not relate to a conjugate form of amphetamine, and is a technically remote document. In view of the teaching of documents (1) and (3) this document cannot be the closest prior art.

9.2.2 Document (3) relates to pharmaceutical compounds that are covalently bound to a chemical moiety and thus rendered pharmaceutically inactive until broken down by enzymatic and/or chemical means in a time-dependent manner following oral administration. Delayed release from the conjugate prevents spiking of drug levels and affords gradual release over an extended period of time. The enzymatic and/or chemical conditions necessary for the release of the controlled substance are either not present or of minimal activity when the novel pharmaceutical compound is administered nasally, inhaled, or administered by injection; thus, spiking is prevented when administration takes these forms. Controlled substances with these novel properties are less likely to be abused due to the diminished "rush" effect of the modified controlled substance. Consequently, the therapeutic value of these pharmaceuticals is enhanced by decreasing euphoria while reducing the duration of the therapeutic effect (see par. [0001]). The problem of document (3) is therefore similar to the problem of the contested patent.

Document (3) envisages *inter alia* an opioid or an amphetamine derivative as a drug susceptible of abuse, but lysine is not explicitly presented as a preferred single amino acid (see par. [0052]-[0053]). Document

(3) discloses in example 7 the compounds GluGlu-amphetamine, Ser-amphetamine and Phe-amphetamine and gives their pharmacokinetic parameters compared to those of amphetamine given alone. It shows that Glu-Glu-amphetamine and Phe-amphetamine have nearly equal C_{max} and AUC to those of the parent drug (see example 7) and that Ser-Amphetamine has a decreased 76% C_{max} and 55% AUC in comparison to oral amphetamine (see Table 5). This document does not disclose directly and unambiguously the compound L-lysine-d-amphetamine.

9.2.3 Document (1) relates to aminocarboxylic acid amides made from amphetamine and from an amino acid which may have its alpha amine function protected (see formulae II and III). This amino acid can be lysine (see page 4 or 7)), and the amphetamine can be d-amphetamine (see page 7). Example 24 discloses a tosyl-protected L-lysine-d-amphetamine and instructions are given in the description of document (1) on how to de-protect such tosyl protected compound (see page 14). This document therefore does not directly and unambiguously disclose the compound L-lysine-d-amphetamine.
The problem of document (1) consists in the provision of compounds which have a high order of anorexogenic activity and a minimum of analeptic activity (see page 16, third par.).

9.2.4 Document (3) thus not only presents a similar technical problem to the claimed invention, but also discloses a combination of features which constitutes the most promising starting point for assessing its obviousness. However, given the partial priority validity of the contested patent, document (3) might constitute the closest prior art only for the subject-matter which benefits only from the most recent priority date, i.e. all subject-matter except the subject-matter of claim

3. Inventive step will therefore be assessed relative to document (1) as well.

9.3 The technical problem to be solved is the provision of an abuse-resistant amphetamine compound that remains therapeutically effective.

9.4 As a solution to this alleged problem, independent claims 1-4 and 16 and 17 of auxiliary request 2 propose the conjugate L-lysine-d-amphetamine and its mesylate or hydrochloride salt.

9.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect. Said alleged effect should be achieved reducing the peak plasma levels whilst simultaneous maintaining the bioavailability of amphetamine when the conjugate is administered orally. Moreover, a non-oral administration prone to amphetamine abuse, such as a nasal or parenteral administration, should lead to a decreased general bioavailability of amphetamine.

9.5.1 Firstly, an effective reduction of the peak plasma levels with simultaneous maintenance of the bioavailability of amphetamine when L-lysine-d-amphetamine is administered orally compared with oral administration of amphetamine, is shown *inter alia* by example 6 and its Table 3 or by Table 15 of the contested patent. These experiments demonstrate clearly and unambiguously the maintenance of the AUC, therefore of the general bioavailability, and the decrease of the C_{max}, and therefore of its linked euphoric effect, through oral administration of Lys-amp in comparison to oral administration of amphetamine as such.

9.5.2 Secondly, decreased bioavailability through nasal or parenteral administration is shown *inter alia* in examples 11, 12, 14 and 15 and corresponding figures 23-26 of the contested patent. These experiments demonstrate a sharp drop in the plasma concentration of amphetamine through its administration in the conjugate form in comparison to the free form, when given through the nasal or parenteral route. These experiments show thus that the conjugate Lys-amp is an abuse- resistant amphetamine compound when taken nasally or parenterally.

9.5.3 Finally, Table 46 of the contested patent shows the pharmacokinetic data of 15 different conjugates of amino acid(s) and amphetamine. The compound Lys-amp is the only conjugate which obtains simultaneously a high AUC percent, namely 98%, and a relative low percent C_{max}, namely 55%, in comparison to what would be obtained through the administration of amphetamine as such. The products disclosed in document (3), namely Glu-Glu-amphetamine, Ser-Amphetamine and Phe-Amphetamine obtain respectively 28% AUC and 74% C_{max}, 79/55% AUC and 62/75% C_{max}, and 95% AUC and 91% C_{max}. These results confirm the data given in example 7 of document (3) as regards the same compounds and show also that these compounds are not suitable for solving credibly the problem posed by the the contested patent. Accordingly, Table 46 proves unambiguously that the administration of Lys-amp allows a simultaneous maintenance of the total bioavailability and a decrease of the C_{max} of amphetamine, and that the claimed conjugate remains therapeutically effective, while diminishing the unwanted side effects or potential abuse.

9.5.4 Hence, in view of the information found in the examples of the contested patent, the board is convinced that the problem defined in point 3.3 above has been plausibly solved.

9.6 It remains to determine whether the solution was obvious to the person skilled in the art.

9.6.1 Document (3) does not envisage the preparation of a conjugate made *inter alia* from an opioid or an amphetamine with lysine as single amino acid; lysine is only mentioned in document (3) as an unwanted amino acid when conjugates with several amino acids are prepared (see par. [052]-[053]).
Moreover, the pharmacokinetic parameters of the amphetamine conjugates of example 7 of document (3) show that the compounds Glu-Glu-amphetamine, Ser-amphetamine and Phe-amphetamine are not simultaneously abuse-resistant and therapeutically as effective as amphetamine. It was furthermore not predictable that replacing the single amino acid conjugates disclosed in example 7 with lysine would provide an effective abuse-resistant amphetamine compound that remains as therapeutically effective as amphetamine.
Hence, the skilled person gets no encouragement from the teaching of document (3) to prepare a conjugate of amphetamine with another single amino acid, still less with lysine.

9.6.2 Document (1) discloses explicitly the compound α-tosyl-L-lysine-d-amphetamine in example 24 and mentions further in the description on page 14 that "A *tosyl group can be removed by the treatment of a so-substituted amide of formula I above with sodium in liquid ammonia*". It also envisages *inter alia* on page 7 of the description a conjugate with lysine and

amphetamine through selection from several lists (see page 7). None of these disclosures however constitute a suggestion or an incentive for preparing Lys-amp, for following reasons:

(a) **The conjugate α-tosyl-L-lysine-d-amphetamine disclosed in example 24 is a final product and not an intermediate product.** There is no suggestion or indication in example 24 that the obtained conjugate must be further de-protected, contrary to what is shown for instance in examples 1 or 2 of D1, wherein a specific de-protection step takes place. The fact that acylated alpha amino acids are indeed final products is further confirmed *inter alia* by the general teaching of D1 on page 9, lines 1 to 10 which mentions that the conjugates of D1 can be obtained by "*removing by conventional techniques such protecting group after the condensation of amphetamine and the alpha-amine carboxylic acid has been effected* ***and thereafter, acylating*** *the product whereby the desired acyl moiety is introduced at the alpha-amino function*". This is also confirmed by the teaching on page 6, line 10 which mentions "N-α-tosyl-L-lysine" as one of the preferred acyl moieties, among other possibilities, such as numerous single L-amino acids, as well as by examples 28 and 29 of D1 which show the preparation of oral dosage forms comprising an α-acyl conjugate.

(b) **The combination of the specific conjugate α-tosyl-L-lysine-d-amphetamine disclosed in example 24 with the feature of the description on page 14 relating to the removal of the tosyl group, in isolation from the remaining general teaching of D1, appears to be based on pure hindsight.** It is not only clear

from the teaching of D1 that the product of example 24 is not intended to undergo a further de-protection step (see point (a) above), but there is no indication on page 14 that a possible de-tosylation should apply specifically to said conjugate of example 24. It is more likely that the de-tosylation disclosed on page 14 had to be applied at least to some of the numerous examples of de-protected conjugates of D1, such as the conjugate D-lysine-d-amphetamine of example 23, for which D1 does not give any detail regarding the process of preparation, or such as the conjugates of examples 13, 15, 16, 17, 19, 21, 23 and 26. The alpha-amino acids of said examples had inevitably to be protected to prepare the conjugate with amphetamine, and an N-alpha tosylation of the amino acid was an option envisaged by D1 (see for instance the description of D1, page 8, lines 4-10).

(c) **In view of the technical problems raised respectively by D1 and by the contested patent, the skilled person would not have any incentive to change the disclosure of D1 to arrive at the subject-matter claimed in auxiliary request 2.** D1 does not deal with the abuse problem and relates to the provision of compounds with a high order of anorexogenic activity and a minimum of analeptic activity (see D1, page 16, third par.). The invention claimed in the contested patent has the opposite aim of providing an abuse-resistant compound which maintains the analeptic activity of amphetamine. Thus, a person skilled in the art would not find any incentive, suggestion or motivation to start with the compound of Example 24 of D1 and modify it to achieve another effect. The

same conclusion applies to the further teaching of D1, for which a selection from a list of amino acids or isomers of amphetamine is necessary (see for instance page 7, 2nd par. to page 8, first par.).

9.6.3 The solution is therefore not obvious to the person skilled in the art from document D3, or from document D1. The subject-matter of claims 1- 17 of auxiliary request 2 involves an inventive step and said auxiliary request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of claims 1 to 17 according to auxiliary request 2, filed with letter of 30 March 2016, and a description to be adapted.

The Registrar: The Chairman:

S. Fabiani A. Usuelli

Decision electronically authenticated