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Datasheet for the decision of 27 September 2018

Case Number: T 0264/16 - 3.3.01

Application Number: 06744466.1

Publication Number: 1863487

IPC: A61K31/4453, A61P25/16, A61P25/28

Language of the proceedings: EN

Title of invention:
TREATMENT OF SYMPTOMS OF PARKINSON'S DISEASE WITH NON-IMIDAZOLE ALKYLAMINES HISTAMINE H3-RECEPTOR LIGANDS

Patent Proprietor:
BIOPROJET

Opponent:
Sölch, Günter

Headword:
Pitolisant/BIOPROJET

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments - added subject-matter (no)
Inventive step - (yes)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 0264/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 27 September 2018

Appellant: (Opponent)	Sölch, Günter Nordring 27 83624 Otterfing (DE)
Representative:	Fachini, Marco Hexal AG Industriestraße 25 83607 Holzkirchen (DE)
Respondent: (Patent Proprietor)	BIOPROJET 30, rue des Francs-Bourgeois 75003 Paris (FR)
Representative:	Lavoix 2, place d'Estienne d'Orves 75441 Paris Cedex 09 (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 1 December 2015 concerning the maintenance of European Patent No. 1863487 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. The present appeal by the opponent (appellant) lies from the interlocutory decision of the opposition division according to which European patent No. 1 863 487 in amended form, based on the claim set filed by the patent proprietor (respondent) on 23 September 2015 and the adapted description filed at oral proceedings on 23 October 2015, and the invention to which it relates, were found to meet the requirements of the EPC.

Independent claims 1 and 3 held allowable by the opposition division read as follow:

"*1. A compound for use in the treatment of excessive daytime sleepiness, associated with Parkinson's disease or obstructive sleep apnea, wherein the compound is selected from 3-(4-chlorophenyl)propyl-3-piperidino-propylether, or its pharmaceutically acceptable salts, hydrates, or hydrated salts, or the polymorphic crystalline structures of this compound or its optical isomers, racemates, diastereoisomers or enantiomers.*"

"*3. A combination comprising a compound as claimed in claim 1 or 2 with an anti-parkinson drug.*"

II. The following documents are referred to in the present decision:

(2) US 2004/0220225

(3) Passani, M.B. et al., TRENDS in Pharmacological Sciences, 25(12), December 2004, 618-625

(4) Meier, G. et al., Arch. Pharm. Med. Chem., 334, Suppl. 2, 2001, Abstract C40

(20) Barbier, A.J. et al., British Journal of Pharmacology, 143, 2004, 649-661

(24) Jucaite, A. et al., International Journal of Neuropsychopharmacology, 16, 2013, 1231-1239

(29) Dauvilliers, Y. et al., The Lancet Neurol., 12, November 2013, 1068-1075

III. In the present decision, the following abbreviations are used:

EDS: Excessive daytime sleepiness
PD: Parkinson's disease
OSA: Obstructive sleep apnea

In addition, the compound cited in claim 1, i.e. 3-(4-chlorophenyl)propyl-3-piperidino-propylether, is referred to by its common name "pitolisant".

IV. The appellant had filed a notice of opposition in which it requested the revocation of the patent pursuant to Article 100(c) and 100(a) EPC (lack of inventive step).

In the appealed decision, the opposition division concluded that the claims filed on 23 September 2015 did not contravene Article 123(2) EPC and that their subject-matter was inventive starting from document (3) as the closest prior art, because pitolisant was not only effective in treating EDS associated with PD or OSA, it did not impair the patient's nocturnal sleep either. The latter effect was derivable from examples 1 and 2 in the patent and had been made credible by the

respondent's experimental data filed on 23 September 2015.

V. The appellant filed notice of appeal against this decision. In the statement of the grounds of appeal, it argued that claims 1 and 3 underlying the decision were contrary to Article 123(2) EPC and that their subject-matter lacked an inventive step over the combination of document (3) with documents (2) and (4).

VI. In its reply to the statement of grounds of appeal, the respondent defended the correctness of the appealed decision.

VII. Oral proceedings were held before the board on 27 September 2018.

VIII. The appellant's arguments, where relevant to the present decision, may be summarised as follows:

On the issue of added subject-matter, the appellant argued that claim 1 contained a new technical teaching because the skilled person had to make a selection from three lists within the content of the application as filed in order to arrive at the claimed subject-matter; claim 1 was the result of choosing a specific compound (pitolisant), a specific disease (PD or OSA) and a specific symptom (EDS). Thus, although pitolisant was mentioned in claim 28, it was not the only compound explicitly mentioned; a whole list of preferred compounds was disclosed in claims 39 and 51. In addition, pitolisant was not specifically disclosed for use in the treatment of EDS associated with PD or OSA: the passage on page 63, lines 20-24, or claim 94, taught its use for treating different diseases without giving any preference to PD or OSA, and the text

running from page 63, line 25 to page 64, line 16, or claim 96, merely disclosed a list of equally preferred symptoms including EDS, which were not linked to the use of pitolisant. The examples did not provide a valid basis for the triple selection either, since they related to the treatment of four different diseases at very specific conditions and only example 1 dealt with EDS. In conclusion, the subject-matter of claim 1 was the result of an intermediate generalisation.

Similarly, the combination in claim 3 was not directly and unambiguously derivable from claim 97, since the latter did not explicitly refer to pitolisant as the compound to be combined with the anti-Parkinson drug.

In its analysis of inventive step, the appellant started from document (3) as the closest prior art because this document was a review article which referred expressly to the use of H_3-receptor antagonists for treating the somnolence syndrome associated with pathological conditions such as PD and OSA (see page 621, right-hand column, lines 5-10).

The subject-matter of claim 1 as considered allowable by the opposition division differed from the disclosure of document (3) in the choice of pitolisant as the H_3-receptor antagonist. This difference was not, however, linked to any unexpected effect. In this respect, the experimental data filed by the respondent on 23 September 2015 to show that treatment with pitolisant did not interfere with the patient's nocturnal sleep could not be taken into consideration because such an effect was not derivable from the application as filed, in particular from its examples. Moreover, neither the data filed on 23 September 2015 nor the patent examples proved that pitolisant did not

interfere with nocturnal sleep because they did not contain comparative data with a control group. In addition, the evidence filed on 23 September 2015 contained no data related to EDS, PD or OSA; it contained exclusively pharmacokinetic data. Lastly, post-published document (29) disclosed in Table 3 that 10% of the patients treated with pitolisant experienced insomnia as an adverse effect. So, the aspect that pitolisant did not interfere with nocturnal sleep could not be introduced into the formulation of the objective technical problem solved by the subject-matter of claim 1, and the problem had to be defined as the provision of an **alternative** H_3-receptor antagonist suitable for treating EDS associated with PD or OSA.

The solution proposed in claim 1 was obvious because documents (2) and (4) disclosed that pitolisant was an H_3-receptor antagonist: document (2) referred to the induction of extended wakefulness in connection with the treatment of central nervous system diseases (see compound 117 on page 58, paragraph [0002], and claims 13 and 17 to 19) and document (4) stressed that pitolisant was one of the most potent H_3-receptor antagonists both *in vitro* and *in vivo*. This obviousness was even clearer in view of the teaching in document (3) that non-imidazole H_3-receptor antagonists were preferred (see page 619, left-hand column, lines 36-39) and from document (20), which disclosed the wake-promoting effect of a non-imidazole H_3-receptor antagonist structurally close to pitolisant and suggested its use for treating EDS associated with *inter alia* sleep apnea (see page 659, right-hand column, last paragraph).

With regard to the issue of inventive step in connection with claim 3, the appellant noted that,

based on the arguments put forward in relation to claim 1, the combination of pitolisant with an anti-Parkinson drug was obvious for treating a subject suffering from PD.

IX. The respondent's arguments, where relevant to the present decision, may be summarised as follows:

On the issue of added subject-matter, the respondent maintained that the application as filed contained pointers to the specific embodiments in claim 1, which were at the core of the invention; they had not been combined artificially. Pitolisant had been individualised as the preferred compound in claim 28 and on page 63, line 17, after the discussion of all other compounds. Subsequently, pitolisant was disclosed on page 63, lines 20-24 for use in the treatment of the symptoms of PD and OSA, which included *inter alia* EDS (see page 63, lines 31-32 and page 64, line 15). This use was also supported by claim 96 in combination with claims 94 and 95. An additional support could be found in examples 1, 2 and 5, which related to the treatment of EDS in patients suffering from PD or OSA.

The combination in claim 3 was supported by claim 97 as filed, in which the preferred compound for combination with the anti-Parkinson drug was pitolisant. This followed from claim 28 and the passage on page 63, lines 20-24.

As regards the assessment of inventive step, the respondent agreed with the appellant that document (3) was the closest prior art and that the subject-matter of claim 1 differed from it in that the H_3-receptor antagonist was pitolisant. It dissented however in the formulation of the technical problem to be solved

which, in its opinion, was the provision of an H_3-receptor antagonist suitable for treating EDS associated with PD and OSA and **which did not interfere with the patient's nocturnal sleep**. This formulation including the prevention of nocturnal sleep impairment was admissible for two reasons: on the one hand, because the application as filed explicitly mentioned this effect in its examples, which stated that pitolisant normalised sleep wakefulness patterns and was able to re-establish a normal sleep architecture (example 1) and that the nocturnal sleep duration was not decreased and its quality was improved (example 2); on the other hand, because the pharmacokinetic data filed on 23 September 2015 showed that pitolisant was substantially cleared from brain and plasma eight hours after oral administration, so that it allowed EDS to be treated without impairing the patient's nocturnal sleep. Regarding the fact that 10% of the patients treated with pitolisant reported in document (29) experienced insomnia as an adverse side-effect, this data was not statistically significant.

Turning to the issue of obviousness, the respondent contended that document (3) cited several H_3-receptor antagonists (see page 619, left-hand column, paragraph 2 and page 622, paragraph bridging both columns) but not pitolisant. In addition, H_3-receptor antagonists had wake-promoting properties and therefore caused insomnia in patients, a problem that was still outstanding in 2013 (see document (24), page 1232, left column, paragraph 2). The induction of insomnia was in fact the main drawback of the H_3-receptor antagonist disclosed in document (20), which was structurally very close to pitolisant but which had a half-life of 13 to 20 hours (see Figure 8 and page 659, penultimate paragraph in document (20) and the figure filed on

21 October 2015). Thus, the finding that pitolisant was suitable to treat EDS in PD or OSA patients without impairing their nocturnal sleep among all H_3-receptor antagonists available at the filing date was unexpected and involved an inventive step. On document (4), the respondent noted that it was less relevant than document (20) because it was only an abstract and dealt with neither EDS nor PD or OSA.

On the issue of inventive step of the combination in claim 3, the respondent referred to the arguments put forward in the discussion of claim 1 and added that the claimed combination aimed in particular at the treatment of PD patients. In this connection, example 4 showed a significant improvement in the symptoms of the patients treated with the combination of claim 3 so that lower doses of the anti-Parkinson drug could be administered.

X. The parties' final requests were as follows:

- The appellant requested that the decision under appeal be set aside and the patent be revoked.

- The respondent requested that the appeal be dismissed, i.e. that the patent be maintained in the version held allowable by the opposition division.

XI. At the end of the oral proceedings, the board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. Added subject-matter - Article 123(2) EPC

2.1 The appellant argued that claim 1 of the only request on file, i.e. the claim 1 held allowable by the opposition division, results from a triple selection within the content of the application as filed, namely the selection of pitolisant as active compound, PD or OSA as disease, and EDS as symptom. The board disagrees.

2.1.1 With regard to the selection of pitolisant as active compound, the application as filed was directed to the use of H_3-receptor antagonists of the formula (A) defined in claim 1 or on pages 4 and 5, for the treatment of PD, OSA, narcolepsy, dementia with Lewis bodies and/or vascular dementia. Preferred compounds of formula (A) were disclosed in claims 2 to 27 or on pages 6 to 57 and in the list on pages 58 to 63. However, the only compound disclosed in the application as a stand-alone preferred embodiment, not embedded within a group or list of other compounds, was pitolisant. This was done in particular in claim 28 and in the passage on page 63, lines 15 to 24, which singled out pitolisant as the preferred active ingredient of formula (A). Beyond that, the preference for pitolisant was reinforced by the fact that it was the only compound cited in connection with an illustrative dose regime on page 66, lines 19 to 23,

and that it was the only compound tested in the application examples. Hence, contrary to the appellant's opinion, the limitation of the compounds of formula (A) to pitolisant does not constitute a selection but merely a restriction to the most preferred compound.

2.1.2 Regarding the choice of diseases and symptom, the board notes that the passage on page 63, lines 20 to 24, disclosed the use of pitolisant for treating the symptoms of five diseases, including PD and OSA. This was also apparent from the combination of claims 94 and 28 as filed. Furthermore, the passage running from page 63, line 25 to page 64, line 26 provided a list of symptoms associated with each of the five cited diseases, including EDS (see page 63, line 31 and page 64, line 15). However, EDS was disclosed only in association with PD or OSA. So, the selection of EDS as the symptom to be treated necessarily implied a restriction of the diseases to PD and OSA. EDS was also taught as one of the preferred symptoms to be treated according to claim 96 as filed. Hence, it was unambiguous from the application as filed that the limitation of claim 1 to the treatment of EDS with pitolisant implicitly contained a limitation of the diseases to PD and OSA. Therefore, that limitation involved only one selection.

2.1.3 In conclusion, the subject-matter of claim 1 results from a single selection within the content of the application as filed.

2.2 Similarly, taking into consideration the argument set out above that pitolisant is the most preferred compound of formula (A) in claim 1 as filed, the subject-matter of claim 3 finds a basis in claim 97 as

filed, which disclosed a combination comprising a compound as claimed in any of its preceding claims with an anti-Parkinson drug.

Insofar as claim 3 is dependent on claim 2, which is limited to the preferred salts of pitolisant, its basis can be found on claim 29 as filed.

2.3 Consequently, the claims held allowable by the opposition division do not contain added subject-matter and fulfil the requirements of Article 123(2) EPC.

3. Inventive step - Article 56 EPC

3.1 The patent is directed to the treatment of patients suffering from EDS associated with PD or OSA with the specific H_3-receptor antagonist pitolisant (see paragraphs [0001] and [0040]).

3.2 It is common ground that document (3) is the closest prior art. This document is a review paper which discloses the waking effect of H_3-receptor antagonists and suggests their use for the treatment of EDS associated with PD or OSA (see in particular the passage on page 621, right-hand column, lines 5-8).

3.3 It is also common ground that the subject-matter of claim 1 underlying the appealed decision differs from the content of document (3) in the selection of pitolisant as H_3-receptor antagonist.

3.4 The technical problem which was solved by the claimed subject-matter was however disputed. While the appellant formulated the problem as the provision of an alternative H_3-receptor antagonist suitable for treating EDS associated with PD or OSA, the respondent

introduced the additional aspect that the H_3-receptor antagonist does not interfere with the patient's nocturnal sleep. It is therefore necessary at this stage to establish the technical problem effectively solved by the subject-matter of claim 1.

Having regard to the fact that the suitability of pitolisant for treating EDS in patients suffering from PD and OSA is not in dispute, the point that needs to be clarified is whether or not the problem may be formulated in the more ambitious form proposed by the respondent. This requires the assessment of two subsequent issues: firstly, whether the aspect that pitolisant does not interfere with the patient's nocturnal sleep is derivable from the application as filed and, if so, whether the solution proposed in claim 1 effectively solves that more ambitious problem.

3.4.1 On the issue of whether the aspect that pitolisant does not interfere with the patient's nocturnal sleep is derivable from the application as filed, the respondent cited examples 1 and 2.

Example 1 discloses the treatment of EDS with pitolisant in a group of cats having induced PD as animal model. The example concludes that the treatment "*is able not only to treat excessive daytime sleepiness ... but also to restablish a normal sleep architecture*" (page 67, lines 24 to 26). From this conclusion, in particular from the fact that pitolisant re-established the normal sleep architecture, the board derives that the application as filed clearly pointed to the fact that pitolisant was effective in treating EDS associated with PD and, at the same time, did not impair the patient's nocturnal sleep.

Example 2 shows the treatment of 10 male patients suffering from OSA with pitolisant, and concludes that the treatment resulted in a clear decrease in the number of diurnal somnolence episodes and a total prevention of the occurrence of diurnal sleep episodes. In other words, pitolisant was suitable for treating EDS in OSA patients. In addition, the example observes that "*the nocturnal sleep duration was not decreased and its quality was improved*" (page 68, lines 5 and 6). In the board's view, this statement unambiguously means that pitolisant did not disrupt the patient's nocturnal sleep.

Hence, in view of examples 1 and 2, the board considers that the aspect that pitolisant does not interfere with the nocturnal sleep of patients suffering from PD or OSA was derivable from the application as filed and therefore may be introduced in the formulation of the technical problem to be solved. Accordingly, the board agrees with the respondent's formulation of the problem as the provision of an H_3-receptor antagonist suitable for treating EDS associated with PD and OSA and which does not interfere with the patient's nocturnal sleep.

3.4.2 Turning to the issue of whether the solution proposed in claim 1 effectively solves the problem posed, in addition to the cited examples, the respondent filed with its letter of 23 September 2015 pharmacokinetic data showing that pitolisant is cleared from mouse or human brain and plasma within 8 hours of oral administration, even when administered at doses as high as 60 mg/kg (see the figures on pages 6 and 7 of the letter). This evidence, linked to the undisputed fact that pitolisant is active in humans at fixed doses of between 20 and 40 mg/once a day (see footnote at the

figure on page 7), leads to the conclusion that the pharmacokinetic data in the letter of 23 September 2015 prove that pitolisant may be administered to a patient in the morning for its waking effect to be exerted during the day, but that the effect will not last so long that it interferes with the patient's nocturnal sleep. Consequently, the board is satisfied that the technical problem as formulated by the respondent is effectively solved by the subject-matter of claim 1.

The appellant argued against this finding that the problem was not solved because Table 3 in document (29) indicated that 10 % of the patients treated with pitolisant experienced insomnia. This argument is, however, not convincing, since the fact that a minority of patients suffering from narcolepsy (not PD or OSA, see the abstract of document (29)) experienced insomnia to a certain extent, cannot counter the fact that the pharmacokinetic profile of pitolisant makes it objectively suitable for treating EDS without disrupting the patient's nocturnal sleep.

3.5 It remains then to be investigated whether or not the proposed solution was obvious to the skilled person at the filing date.

As explained in point 3.2 above, document (3) discloses the waking effect of H_3-receptor antagonists and suggests their use for the treatment of EDS associated with PD or OSA. In this context, the document mentions several H_3-receptor antagonists, such as GT2331, ciproxifan, A3041121 and A317920, but fails to cite pitolisant, which was nevertheless known as a potent H_3-receptor antagonist at least three years before the publication of document (3) (see document (4)). Besides, document (20) discloses an H_3-receptor

antagonist structurally close to pitolisant which confirms the teaching in document (3) that H_3-receptor antagonists have a wake-promoting effect.

What documents (3) and (20) apparently do not take into consideration is the fact that the suitability of a wake-promoting compound to treat sleep disorders such as EDS is inherently linked to the duration of its effect, which should be limited to the period of time within which the patient needs to be awake; an effect beyond those hours is undesired since it disrupts the patient's nocturnal sleep. Thus, although document (3) discloses the wake-promoting effect of H_3-receptor antagonists, this effect is a necessary but not a sufficient condition for suitably treating EDS; suitable compounds must in addition not impair the patient's nocturnal sleep. However, document (3) does not contain any information in this respect. Further, document (20) states that its H_3-receptor antagonist has a relatively long half-life of 13 to 20 hours (see page 659, right-hand column, paragraph 4), a fact that could possibly lead to a disruption to the patient's nocturnal sleep.

With regard to the combination of documents (3) or (20) with documents (2) or (4) the board comes to the following conclusions:

Document (2) discloses a family of H_3-receptor antagonists as potential active ingredients for *inter alia* inducing extended wakefulness (see paragraph [0002] to [0004] and claim 19). Among other compounds, the document discloses pitolisant (see compound 117 on page 58 and claims 13, 16 and 18). Document (4) discloses pitolisant as a potent H_3-receptor antagonist

and suggests its use in the treatment of attention deficit hyperactivity disorder and Alzheimer's disease.

Thus, at the filing date, it was known that H_3-receptor antagonists were good candidates for *inter alia* inducing extended wakefulness. It was also known that pitolisant was an H_3-receptor antagonist. However, other H_3-receptor antagonists were also known and the prior art did not contain any information on which of them could effectively promote wakefulness without impairing the patient's nocturnal sleep. Hence, there was no pointer for the skilled person to select pitolisant as the particular H_3-receptor antagonist suitable for treating EDS in patients suffering from PD or OSA without disrupting their nocturnal sleep.

For these reasons, the board concludes that pitolisant was not an obvious solution to the problem posed. Hence, its use for the treatment of EDS associated with PD or OSA is inventive.

3.6 On the issue of inventive step in connection with claim 3, considering that the use of pitolisant for treating EDS associated with PD is inventive, its combination with an anti-Parkinson drug is also inventive. This results from the fact that the prior art contains no pointer that this combination would be particularly suitable for treating both PD and its associated EDS without impairing the patient's nocturnal sleep.

3.7 Consequently, the claims held allowable by the opposition division fulfil the requirements of Article 56 EPC.

4. Since the objections raised by the appellant in appeal proceedings are not convincing, the board has no reason to set aside the decision under appeal.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated