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Datasheet for the decision of 7 November 2023

Case Number: T 0963/20 - 3.3.07

Application Number: 16187426.8

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Language of the proceedings: EN

Title of invention:
NALMEFENE FOR REDUCTION OF ALCOHOL CONSUMPTION IN SPECIFIC TARGET POPULATIONS

Patent Proprietor:
H. Lundbeck A/S

Opponent:
Alfred E. Tiefenbacher (GmbH & Co. KG)

Headword:
Nalmefene/LUNDBECK

Relevant legal provisions:
EPC Art. 54(5), 56

Keyword:
Novelty - novelty of second (or further) medical use - group of patients
Inventive step - (no)

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Case Number: T 0963/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 November 2023

Appellant: (Opponent)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	H. Lundbeck A/S Ottiliavej 9 2500 Valby (DK)
Representative:	Potter Clarkson Chapel Quarter Mount Street Nottingham NG1 6HQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 March 2020 rejecting the opposition filed against European patent No. 3138564 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	Y. Podbielski

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision rejecting the opposition filed against European patent No. 3138564.

II. The patent was granted with 14 claims. Claim 1 was the only independent claim and read as follows.

"*1. Nalmefene for use in the treatment of alcohol dependence in a patient with alcohol dependence, wherein said use reduces alcohol consumption; wherein said patient with alcohol dependence:*

has a DRL (drinking risk level) corresponding to consumption >60g/day of pure alcohol for men and >40g/day for women;
wherein said patient maintains a DRL corresponding to consumption >60g/day of pure alcohol for men and >40g/day for women after an observation period following initial assessment;
and wherein said observation period following initial assessment is 1-2 weeks such as about 2 weeks."

III. The following documents cited by the parties during the opposition and appeal proceedings are referred to in this decision.

D1a Summary of product characteristics for Selincro 18 mg film-coated tablets, European Medicines Agency, no publication date

D2 Guideline on the development of medicinal products for the treatment of alcohol dependence, European Medicines Agency, 18 February 2010

D4 S. Karhuvaara et al., Alcoholism: Clinical and Experimental Research, 31(7), 2007, 1179-1187

IV. In the decision under appeal, the opposition division found, among other things, that the subject-matter of claim 1 as granted was novel and inventive starting from D4 as the closest prior art.

V. The opponent (appellant) filed an appeal against the decision. In its statement of grounds of appeal, the appellant requested that the decision be set aside and that the patent be revoked in its entirety.

VI. In its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed.

VII. The Board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

VIII. In response to the Board's preliminary opinion, the respondent filed auxiliary request 1, which differed from the main request (patent as granted) in that the dependent claims had been deleted.

IX. Oral proceedings were held before the Board on 7 November 2023. At the end of the oral proceedings, the Board announced its decision.

X. The appellant's arguments relevant to the present decision can be summarised as follows.

Novelty over D4

D4 disclosed treating heavy drinkers with nalmefene to help reduce their alcohol consumption. The patients in D4 had problems controlling their drinking and 93% of them were diagnosed as alcohol dependent. Based on their alcohol consumption, disclosed in Table 2, it could be inferred that the patients in D4 had a high DRL. There was therefore a great overlap between the population treated in D4 and the patient group of claim 1. The latter was not clearly identified by a new marker, and it did not reflect a new clinical situation either. Consequently, the subject-matter of claim 1 could not be distinguished from the disclosure of D4.

Inventive step

D4 was the closest prior art. If the patient group of claim 1 was novel over D4 and responded better to the treatment with nalmefene, the objective technical problem was as proposed by the Board in its preliminary opinion, i.e. finding a group of alcohol-dependent patients which particularly benefits from treatment with nalmefene.

The patients in claim 1 could not sufficiently reduce their DRL without the aid of a pharmacological treatment. Considering common general knowledge, these patients had to be those with higher physiological alcohol dependence for two reasons. First, chronic drinking produced a physiological dependence caused by neuroadaptive changes in the brain which induced the craving for alcohol (D2, point 1.4). Second, nalmefene

reversed the changes in the brain produced by chronic drinking and helped to reduce the craving for alcohol (patent, paragraphs [0003] and [0004]).

D2 disclosed the EMA guideline for clinical studies on alcohol dependence. It suggested (point 4.1.1, last paragraph) stratifying patients according to their level of physiological dependence. Therefore, the skilled person would stratify the patients in D4 as suggested by D2. They would then find that the patients with greater physiological alcohol dependence exhibited a greater response to nalmefene treatment. Consequently, the subject-matter of claim 1 did not involve an inventive step.

XI. The respondent's arguments relevant to the present decision can be summarised as follows.

Novelty over D4

The subject-matter of claim 1 differed from D4 in the treated patient group, which was characterised by the test in claim 1. It could not be concluded from Table 2 of D4 that the treated patients had a high DRL. Furthermore, D4 did not disclose any monitoring of patients during the period between screening and randomisation, let alone an observation of their reduction in DRL.

Contrary to the appellant's view, there was no obligation to use a biochemical marker to define a new patient group. The functional definition was justified in this case because there was no other way to characterise the patients of the invention, who had a particular pathological state: they were at high risk of health-related harm and could not sufficiently

reduce alcohol consumption on their own. Table 5 of the patent showed that the patients of claim 1 constituted a subgroup within the population of patients with a high DRL. In addition, Table 6 showed that they exhibited a greater response to nalmefene treatment. Therefore, the patient group of claim 1 was novel over D4.

Inventive step

The subject-matter of claim 1 differed from D4 as the closest prior art in the patient group treated. The patients of claim 1 were characterised by a pathological state that was associated with a greater response to nalmefene.

The objective technical problem was the provision of a particularly effective treatment for patients with particularly heavy alcohol consumption.

The patients of claim 1 were neither those with the highest DRL nor those with the highest alcohol dependence. For instance, the majority of the patients according to claim 1 in the clinical studies of the patent had low to moderate alcohol dependence (D1a, page 9, second paragraph). The only way to arrive at the patients of claim 1 was to carry out the required test. Therefore, stratification according to the patients' level of alcohol dependence, as suggested in D2, would not lead to the claimed subject-matter. No cited prior art suggested that the patients who maintain a high DRL after an observation period of one to two weeks after initial assessment responded better to treatment with nalmefene. Therefore, the subject-matter of claim 1 was inventive.

XII. The parties' final requests were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant also requested that auxiliary request 1, filed by the respondent with its letter dated 15 September 2023, not be admitted into the appeal proceedings.

- The respondent requested that the appeal be dismissed and that the patent be maintained as granted (main request) or, alternatively, that the patent be maintained in amended form on the basis of auxiliary request 1 as filed with its letter dated 15 September 2023.

Reasons for the Decision

1. Technical background

The patent is concerned with the use of nalmefene for reducing alcohol consumption in alcohol-dependent patients who have a high DRL (drinking risk level) and maintain that high DRL after an observation period of one to two weeks following initial assessment.

The DRL is an estimation of the risk that drinking entails for patient health. It is assessed by calculating the mean daily alcohol consumption in g/day over a time period of at least one week. According to the patent, a high DRL is associated with the consumption of more than 60g/day pure alcohol for men and more than 40g/day for women. These ranges are in

line with those defined by the WHO (patent, paragraphs [0013] to [0015]).

The invention in claim 1 is based on observations derived from three clinical studies. The studies showed that a significant number of patients with a high DRL at initial assessment considerably reduced their alcohol consumption during an observation period of one to two weeks following that initial assessment. Those patients were called "early reducers" (ERs). The studies also showed that the response to nalmefene in the population of patients excluding ERs was greater than in the total population treated: non-ERs reduced the number of heavy-drinking days (HDDs) and total alcohol consumption (TAC) to a larger extent (patent, paragraphs [0016], [0034] and [0035]).

Based on these results, claim 1 was directed to the treatment of non-ERs with nalmefene.

2. Novelty over D4 - claim 1 as granted

2.1 Document D4 discloses (abstract; page 1182, left-hand column, second paragraph; and page 1186, left-hand column, third paragraph) the results of a clinical study on treatment with nalmefene for reducing heavy drinking. The participants in the study were regular drinkers with difficulties in controlling their drinking. 93% of them were diagnosed as alcohol dependent. The majority of the participants were abstinent for fewer than 30% of days and their drinking days were typically HDDs. Their monthly alcohol consumption during the 12 weeks preceding screening was detailed in Table 2 of D4. This amounted to a weighted average of 75g/day of pure alcohol (total alcohol consumption of 43.9 drinks/week, 1 drink being 12g of

pure alcohol; D4, page 1181, left-hand column, third paragraph), distributed across 15.8 HDDs and 8.5 very heavy drinking days (VHDDs) per month. The weighted average number of abstinence days was 8.7 per month.

The definition of a HDD in D4 (page 1181, left-hand column, third paragraph) is similar to the one in the patent (paragraph [0011]), namely a day with a consumption of 60g or more pure alcohol for men and 48g or more for women. A VHDD was a day with a consumption of 120g or more pure alcohol for men and 96g or more for women.

In light of the data on alcohol consumption in Table 2, the Board agrees with the appellant that it can be concluded that a majority of the participants in the clinical study of D4 had a high DRL before starting the treatment with nalmefene, i.e. the men consumed more than 60g/day of pure alcohol and the women more than 40g/day. This means that there was a significant overlap between the population at initial assessment in D4 and that in claim 1, and that they can be considered similar.

2.2 Unlike claim 1, D4 does not disclose an observation period during which changes in the participants' alcohol consumption are monitored between the initial assessment and the start of the treatment. This means that D4 does not discriminate between ERs and non-ERs in the population of patients with a high DRL, while claim 1 is limited to the treatment of non-ERs (see point 1 above). Therefore, the issue of novelty over D4 hinges on whether the treatment of non-ERs can be distinguished from the treatment of the population of patients with a high DRL at initial assessment.

Table 5 of the patent specifies for each of the three clinical studies carried out the number of patients with high DRL at initial assessment (i.e. at baseline) and the number of patients maintaining a high DRL after an observation period of two weeks according to claim 1 (i.e. at baseline and randomisation). The relevant information is reproduced in the table below.

Study	Population	Placebo	Nalmefene
12014A	High DRL at baseline	230	222
	High DRL at baseline and randomisation	167	171
12023A	High DRL at baseline	247	265
	High DRL at baseline and randomisation	155	148
12013A	High DRL at baseline	88	252
	High DRL at baseline and randomisation	42	141

It is apparent from the table that, in the three studies, the number of patients with a high DRL after the observation period is significantly lower than at initial assessment, namely between half and three quarters of the latter. The patients according to claim 1 constitute a subgroup within the population of patients with a high DRL at initial assessment.

In addition, Table 6 of the patent shows that the patients with a high DRL after the observation period

respond better to a six-month treatment with nalmefene than the total population with a high DRL at initial assessment. The relevant data are summarised in the table below.

Study	Endpoint	Population	Mean difference to placebo in the change from baseline
12014A	HDD	High DRL at baseline	-2.6 days/month
		High DRL at baseline and randomisation	-3.7 days/month
	TAC	High DRL at baseline	-12.2 g/day
		High DRL at baseline and randomisation	-18.3 g/day
12023A	HDD	High DRL at baseline	-2.1 days/month
		High DRL at baseline and randomisation	-2.7 days/month
	TAC	High DRL at baseline	-6.6 g/day
		High DRL at baseline and randomisation	-10.3 g/day
12013A	HDD	High DRL at baseline	-1.1 days/month
		High DRL at baseline and randomisation	-2.6 days/month

	TAC	High DRL at baseline	-5.6 g/day
		High DRL at baseline and randomisation	-15.3 g/day

It follows from these data that the reduction in alcohol consumption compared with the placebo in the group of patients according to claim 1 is significantly greater than in the total population of patients with a high DRL at initial assessment. On average, the patients according to claim 1 reduced their alcohol consumption in roughly 1 HDD/month and by 6g/day more than the total population. This difference in response suggests that the patients according to claim 1 are characterised by a particular pathological or physiological state related to the pharmacological effect of nalmefene.

Since the population treated in D4 can be considered similar to the group of patients with a high DRL at baseline (see point 2.1 above), the Board agrees with the respondent that the patient group of claim 1 is a selection which is not disclosed in D4 and which results in a new clinical situation due to the pathological or physiological state of the selected patients.

2.3 Therefore, the subject-matter of claim 1 is novel over D4 (Article 54 EPC).

3. Inventive step - claim 1 as granted

3.1 The parties agreed that D4 is a suitable starting point for the assessment of inventive step.

As discussed with respect to novelty, the subject-matter of claim 1 differs from the treatment with nalmefene in D4 in terms of the selected patient group. The patients of claim 1 are alcohol-dependent patients with a high DRL at initial assessment and maintaining a high DRL after an observation period of one to two weeks following initial assessment.

It was undisputed that the technical effect associated with this difference is that the patients of claim 1 respond better to the treatment with nalmefene; they achieve a greater reduction of their TAC (see point 2.2 above).

3.2 Based on this effect, the respondent defined the objective technical problem in the same way as in the decision under appeal, i.e. the provision of a particularly effective treatment for patients with particularly heavy alcohol consumption. This definition of the problem, however, is not fully in line with the respondent's position that the patients in claim 1 are not those with the highest DRL.

In the Board's view, the objective technical problem is, rather, finding a group of alcohol-dependent patients which benefits particularly from treatment with nalmefene. This definition of the problem was adopted by the appellant at the oral proceedings before the Board.

The Board is satisfied that the patient group selected by the test of claim 1 is a solution to the problem posed. This is apparent from the results of the clinical studies reported in Table 6 of the patent, which show that the patients according to claim 1 respond better to nalmefene treatment than the average

population with a high DRL at initial assessment, which is similar to the population tested in D4 (see also point 2.2 above).

3.3 The patient group of claim 1 is defined functionally by means of a test. However, it cannot be excluded that the skilled person could arrive at the same patient group by other means. Therefore, to assess whether the skilled person would arrive at the subject-matter of claim 1 in an obvious way, it is necessary to investigate the physiological or pathological state that characterises the patients of claim 1.

3.3.1 The patent does not provide any information in this respect. It is silent on why some patients reduce their alcohol consumption during the observation period after initial assessment while others do not.

The respondent's submissions during the appeal proceedings did not provide clarification either. The respondent merely repeated the definition in claim 1, stating that the selected patients were those who were not able to reduce their alcohol consumption below a high DRL during the observation period. According to the respondent, the selected patients could not be defined in any other way; they had neither the highest DRL nor the highest alcohol dependence.

3.3.2 In contrast, the appellant gave a technically sensible explanation based on common general knowledge that the Board found convincing.

The appellant noted first that a reduction of alcohol consumption during the observation period can only be driven by motivation, since the patients have not yet started pharmacological treatment. Then, the appellant

referred to common general knowledge in the treatment of alcohol dependence. The cited common general knowledge was not disputed by the respondent.

The appellant cited D2 (page 5, point 1.4) to explain that chronic drinking leads to neuroadaptive changes in the brain which induce an alcohol craving and cause alcohol dependence. These changes involve, among other things, the opioidergic system. The appellant also referred to the common general knowledge that, as disclosed in paragraphs [0003] and [0004] of the patent, nalmefene was developed for managing alcohol dependence due to its ability to reverse the effects of opioid agonists. In paragraph [0004], the patent cites D4 as a report of a clinical study showing the positive effect of nalmefene in patients craving alcohol.

Consequently, it can be concluded from the common general knowledge that the patients selected by the test of claim 1 are those whose neuroadaptive changes in the brain are of such a nature or extent that the patients cannot control their craving for alcohol sufficiently in the absence of pharmacological aid. In other words, the pathological state that characterises the patients of claim 1 within the total population of patients with a high DRL is a higher physiological alcohol dependence caused by neuroadaptive changes in the brain.

3.3.3 The respondent replied that D1a (page 9, second paragraph) explains the characteristics of the patients tested in the patent, and that the majority of them had low to moderate alcohol dependence. Therefore, the patients of claim 1 were not those with the highest alcohol dependence.

However, the Board notes that having a low to moderate alcohol dependence is not incompatible with the fact that the patients selected through the observation period of claim 1 are those with the higher physiological dependence within the initial population with a high DRL, irrespective of their absolute alcohol dependence.

3.3.4 Having established the pathological state characterising the patient group of claim 1, it is now necessary to assess whether the skilled person would arrive at that patient group in an obvious way. The prior art cited in this context was D2, the guideline of the European Medicines Agency on the development of medicinal products for the treatment of alcohol dependence.

D2 suggests in point 4.1.1, last paragraph, that the patients in clinical studies on alcohol dependence be stratified by their alcohol dependence. It proposes measuring the level of dependence using validated instruments such as the Severity of Alcohol Dependence Questionnaire, the Alcohol Dependence Scale or the Addiction Severity Index. As explained above (point 3.3.2), alcohol dependence within the meaning of D2 is the physiological dependence caused by the neuroadaptive changes that alcohol produces in the brain.

Therefore, the skilled person seeking a group of patients who benefit particularly from the treatment with nalmefene would stratify the results of the clinical study on alcohol dependence in D4 according to patients' physiological dependence. In this way, they would find that the patients who benefit the most from treatment with nalmefene are those with a greater

physiological alcohol dependence, i.e. the patients selected by the test of claim 1.

3.4 Therefore, contrary to Article 56 EPC, the subject-matter of claim 1 does not involve an inventive step.

4. Auxiliary request 1

Claim 1 of auxiliary request 1 is identical to claim 1 as granted. Therefore, irrespective of its admissibility, the subject-matter of auxiliary request 1 lacks an inventive step (Article 56 EPC) for the same reasons as those set out with respect to the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated