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Datasheet for the decision of 11 January 2024

Case Number: T 0025/20 - 3.3.02

Application Number: 10831895.7

Publication Number: 2501234

IPC: A01N43/62, A61K31/55, A61P25/20, A61P25/22

Language of the proceedings: EN

Title of invention:
METHODS AND COMPOSITIONS FOR TREATING SYMPTOMS ASSOCIATED WITH POST-TRAUMATIC STRESS DISORDER USING CYCLOBENZAPRINE

Patent Proprietor:
Tonix Pharma Holdings Limited

Opponent:
Kraus & Lederer PartGmbB

Relevant legal provisions:
EPC Art. 100(b), 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0002/21, T 0950/13

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Case Number: T 0025/20 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 11 January 2024

Appellant: (Opponent)	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Patent Proprietor)	Tonix Pharma Holdings Limited Canon's Court 22 Victoria Street Hamilton, HM 12 (BM)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 October 2019 rejecting the opposition filed against European patent No. 2501234 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	L. Bühler

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent (appellant) against the opposition division's decision (decision under appeal) to reject the opposition against European patent No. 2 501 234 (patent).

II. Reference is made in the present decision to the following document filed with the opposition division:

D12 Poster entitled "A Randomized Placebo-Controlled Multicenter Trial of a Low-Dose Bedtime Sublingual Formulation of Cyclobenzaprine (TNX-102 SL*) for the Treatment of Military-Related PTSD"

III. With the reply to the statement of grounds of appeal, the patent proprietor (respondent) filed the sets of claims of auxiliary requests 1 and 2.

IV. In preparation for the oral proceedings, which had been arranged at the parties' request, the board issued a communication pursuant to Article 15(1) RPBA.

V. The oral proceedings before the board were held by videoconference on 11 January 2024 in the presence of both parties. At the end of the oral proceedings, the chair announced the order given in the present decision.

VI. The parties' final requests at the end of the oral proceedings were as follows:

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.
- The respondent requested that the appeal be dismissed, implying that the decision under appeal be confirmed and the patent be maintained as granted (main request). In the alternative, the respondent requested that the patent be maintained in amended form based on one of the sets of claims of auxiliary requests 1 or 2, filed with the reply to the statement of grounds of appeal.

VII. The appellant's arguments on the allowability of the main request and auxiliary requests 1 and 2, in so far as relevant to the present decision, can be summarised as follows:

- Examples 1 and 2 of the application as filed described the manufacture of a tablet and a gelcap formulation comprising cyclobenzaprine, respectively. Example 3 described a protocol for a study of the effect of the gelcap formulation from example 2 on patients suffering from post-traumatic stress disorder (PTSD). The fact that it was written in the future tense made it clear that the study had yet to be conducted. Examples 4 to 6 simply described what a treatment for PTSD should ideally look like. They were prophetic. Therefore the application as filed did not contain any experimental evidence for the suitability of cyclobenzaprine for the treatment of PTSD.
- The mechanistic explanation provided by the respondent was not disclosed in the application as filed, but was a narrative provided only after the effective date of the patent.

- The application as filed lacked any specificity for cyclobenzaprine, which could simply be replaced by any other drug.
- The invention as defined in claims 1 and 6 of the main request and of auxiliary requests 1 and 2 rested on the well-known suitability of cyclobenzaprine to treat sleep disturbances in a variety of conditions other than PTSD. It could not credibly be deduced from this that cyclobenzaprine was also suitable for treating sleep disturbances associated with PTSD, as there were some drugs, such as cyproheptadine and certain benzodiazepines, that were not suitable for such treatment but were suitable for the treatment of sleep disturbances associated with other conditions.

VIII. Summaries of the respondent's arguments on the allowability of the main request and auxiliary requests 1 and 2, in so far as relevant to the present decision, are contained in the reasons for the decision.

Reasons for the Decision

Main request (patent as granted) - sufficiency of disclosure

1. Independent claims 1 and 6 as granted read as follows (emphasis in bold added):

Claim 1

"*A pharmaceutical composition comprising cyclobenzaprine in a therapeutically effective amount and a therapeutically effective carrier, for use in a method for treating* ***the development of a post-traumatic stress disorder (PTSD) symptom, or***

the initiation of a PTSD symptom, or the consolidation of a PTSD symptom, or the perpetuation of a PTSD symptom following a traumatic event *comprising administering to a human in need of such treatment said pharmaceutical composition, wherein such treatment eliminates or ameliorates the PTSD symptom, wherein the therapeutically effective amount of cyclobenzaprine administered is between 0.5 mg and 50 mg/day.*"

Claim 6

"*A pharmaceutical composition comprising cyclobenzaprine in a therapeutically effective amount and a therapeutically effective carrier for use in a method for treating* ***a sleep disturbance or a non-sleep disturbance associated with post-traumatic stress disorder (PTSD)*** *comprising administering to a human in need of such treatment said pharmaceutical composition, wherein such treatment ameliorates or eliminates the non-sleep disturbance, wherein the therapeutically effective amount of cyclobenzaprine administered is between 0.5 mg and 50 mg/day.*"

1.1 Claims 1 and 6 thus relate to second medical uses of a composition comprising cyclobenzaprine. They differ essentially in terms of the therapeutic effect to be achieved (in bold above). Claim 1 relates to the treatment of the initiation, consolidation or perpetuation of a PTSD symptom or, in short, the development of a PTSD symptom, following a traumatic event (according to paragraph [0011] of the patent, the phases initiation, consolidation and perpetuation are summarised under the term development). Claim 6 relates

to the treatment of a sleep or a non-sleep disturbance associated with PTSD.

1.2 The parties agreed that a sleep disturbance associated with PTSD, as recited in claim 6, is a PTSD symptom within the meaning of claim 1 and that, therefore, not only claim 6 but also claim 1 covers, *inter alia*, the treatment of a sleep disturbance associated with PTSD.

2. The application as filed (page 1, line 18 to page 2, line 17, corresponding to paragraphs [0002] and [0003] of the patent) states that cyclobenzaprine is suitable for the treatment of a variety of sleep disturbances. Those mentioned in the patent are associated with conditions other than PTSD. The patent also states that disturbed sleep is a central feature of PTSD. The parties agreed that these points are common general knowledge.

3. In the course of the present appeal proceedings, the Enlarged Board of Appeal (EBA) issued its decision G 2/21. The EBA held (emphasis added):

> "*The reasoned findings of the boards of appeal in the decisions referred to above make clear that the scope of reliance on post published evidence is much narrower under sufficiency of disclosure (Article 83 EPC) compared to the situation under inventive step (Article 56 EPC).* ***In order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to***

the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence."

4. The parties disagreed, *inter alia*, as to whether sleep disturbances associated with PTSD - a condition covered by claims 1 and 6 according to both parties (see point 1.2 above) - can credibly be treated with a composition comprising cyclobenzaprine.

5. Experimental evidence of the therapeutic effect

Examples 1 and 2 of the application as filed disclose the manufacture of pharmaceutical compositions comprising cyclobenzaprine. Example 3 describes a protocol for a study still to be conducted with the composition of example 2. Example 3 does not report on any results. Lastly, examples 4 to 6 describe what the treatment of PTSD with cyclobenzaprine should ideally look like and, as accepted by the respondent, are purely prophetic in nature.

In view of this, the parties agreed that the application as filed does not contain any experimental evidence relating to the therapeutic effect in question.

6. Credible technical concept

6.1 The respondent pointed to what is set out as common general knowledge in the application as filed, namely that cyclobenzaprine is suitable for the treatment of sleep disturbances associated with a variety of conditions other than PTSD and that disturbed sleep is a central feature of PTSD (see point 2 above). Against this background, the application as filed (page 7,

line 15 to page 9, line 2, corresponding to paragraphs [0011] and [0012] of the patent) disclosed a credible technical concept in the form of the underlying mode of action of cyclobenzaprine. More specifically, cyclobenzaprine improved the sleep quality of PTSD patients in a manner that enabled them to process the memories of their psychological trauma during sleep, thereby alleviating the sleep disturbances associated with PTSD. Examples 4 to 6 of the application as filed also described mechanistically what happened when cyclobenzaprine was taken.

6.2 In its decision, the opposition division agreed with this analysis and ultimately acknowledged sufficiency of disclosure.

6.3 The passage of the application as filed relied on by the respondent (page 7, line 15 to page 9, line 2) first sets out what types of events are to be considered a traumatic event, i.e. an event which is so severe that it can trigger PTSD. This is followed by a description of the development of PTSD over time after such a traumatic event, the development being divided into three phases according to the time elapsed after the traumatic event: initiation, consolidation and perpetuation. The application as filed then goes on to explain when cyclobenzaprine should be administered to be effective in each phase. However, contrary to the respondent's argument, there is no reference to the mode of action of cyclobenzaprine in this passage. The same applies to the prophetic examples 4 to 6, which merely describe phenomenologically what a treatment with cyclobenzaprine should ideally look like.

It must therefore be concluded that the purported mode of action of cyclobenzaprine relied on by the

respondent as a technical concept supporting the achievement of the claimed therapeutic effect is not disclosed in the application as filed.

6.4 The board wishes to add that even if the respondent's purported mode of action of cyclobenzaprine were disclosed verbatim in the application as filed such a disclosure would still not be tantamount to a credible technical concept, for the following reasons.

The application as filed does in fact not demonstrate any mode of action of cyclobenzaprine. With regard to the therapeutic effect at issue, i.e. the treatment of sleep disturbances associated with PTSD, there are no investigations or explanations setting cyclobenzaprine apart from other drugs. There is no teaching as to what exactly makes a compound, let alone cyclobenzaprine, suitable for the treatment of sleep disturbances associated with PTSD. The application as filed lacks any specificity in relation to cyclobenzaprine: the word "cyclobenzaprine" could simply be replaced by the name of any other drug. Ultimately, this means that the credibility of the purported mode of action of cyclobenzaprine, and with it the credibility of the technical concept, rests only on the well-known property of cyclobenzaprine set out in the application as filed, i.e. its suitability for the treatment of sleep disturbances associated with various conditions other than PTSD.

As the respondent emphasised, drugs such as prazosin can be used to treat both sleep disturbances associated with PTSD and those unrelated to PTSD. At the same time, however - and this was acknowledged by the respondent - it was well-known before the effective date of the patent that compounds such as

cyproheptadine and certain benzodiazepines (alprazolam, temazepam) were not suitable for treating sleep disturbances associated with PTSD despite their otherwise positive effect on sleep disturbances associated with various other conditions.

With compounds having a positive effect on sleep disturbances associated with various conditions other than PTSD, some of them being suitable for the treatment of sleep disturbances associated with PTSD and some not, it must be concluded that the purported mode of action of cyclobenzaprine merely amounts to a guess - a guess as to how cyclobenzaprine might work and that it would be suitable for the treatment of sleep disturbances associated with PTSD. Such a guess does not make the purported mode of action of cyclobenzaprine or the technical concept built on it credible.

Instead, in view of the considerations above, it must be concluded that there are substantiated doubts in the present case about the credibility of the purported mode of action of cyclobenzaprine and the technical concept based on it.

7. At the oral proceedings before the board, the respondent pointed to decision T 950/13.

7.1 In that case, the claim at issue was directed to the use of dasatinib in the manufacture of a medicament for the treatment of chronic myelogenous leukemia (CML). The application as filed did not contain experimental evidence but disclosed that dasatinib was an inhibitor of BCR-ABL kinase. The inhibition of this kinase was accepted in the art as an effective way to treat CML. Furthermore, the application as filed drew an analogy

with imatinib, another effective inhibitor of BCR-ABL kinase, which had been approved for the treatment of CML well before the filing date of the application. The competent board was satisfied

> "*that the application discloses at least a plausible technical concept, namely that dasatinib based on its functional equivalence to imatinib as a BRC-ABL* [sic] *kinase inhibitor is suitable in the treatment of CML. There are no reasons apparent to the board as to why a skilled person would a priori regard this teaching as incredible or implausible.*" (T 950/13, point 3.6 of the Reasons)

7.2 According to the respondent, the situation in the present case was analogous to that underlying T 950/13. In both cases, the application as filed did not contain experimental evidence. Nevertheless, in each case the mode of action of the drug was disclosed. Hence credibility of the technical concept should also be acknowledged in the present case.

7.3 However, the purported mode of action of cyclobenzaprine in the present case is not a mechanism at the molecular level which is of generally recognised importance for the disease or the symptom to be treated. Instead, the application as filed offers as support for the purported mode of action merely the known suitability of cyclobenzaprine for treating sleep disturbances associated with various conditions other than PTSD. As explained above, this suitability alone is not sufficient to establish credibility in the present case because there are substantiated doubts about the purported mode of action and the technical concept based on it. This sets the present case apart

from T 950/13, in which the competent board did not identify such doubts (see quote above).

8. In the absence of a credible technical concept, the mere allegation in the application as filed that cyclobenzaprine is suitable for treating sleep disturbances associated with PTSD, as covered by both claims 1 and 6, is a mere statement which is not enough to ensure sufficiency of disclosure. This lack of sufficiency cannot be remedied by post-published evidence D12, which the respondent considered proof of the therapeutic effects recited in claims 1 and 6.

Thus the invention as defined in claims 1 and 6 of the main request is insufficiently disclosed.

Auxiliary requests 1 and 2 - sufficiency of disclosure

9. Compared with claims 1 and 6 of the main request, claims 1 and 6 of auxiliary request 1 additionally specify that the composition comprising cyclobenzaprine is "*for use in a method of treating or preventing post-traumatic stress disorder (PTSD)*". Claims 1 and 6 of auxiliary request 2 additionally require that the composition with cyclobenzaprine be administered to a human "*with PTSD*".

10. These additional features were included by the respondent to overcome some of the appellant's novelty objections. More specifically, the additional feature in auxiliary request 1 was intended to make it clearer that the claims relate to PTSD (and not also to other diseases). The additional feature in auxiliary request 2 was intended to limit the claims to a patient already suffering from PTSD (thereby excluding preventive treatments).

11. However, the assessment of the main request above focused on the treatment of sleep disturbances associated with PTSD, i.e. a symptom of PTSD in a patient already suffering from PTSD. Thus the assessment of the main request above equally applies to both auxiliary requests 1 and 2.

In line with this, the board explained at the oral proceedings that the same conclusion on sufficiency of disclosure as for the main request applied to auxiliary requests 1 and 2. This was not disputed by the respondent, nor did it put forward any arguments in this respect.

12. Thus the invention defined in claims 1 and 6 of auxiliary requests 1 and 2 is insufficiently disclosed. Accordingly, auxiliary requests 1 and 2 are not allowable.

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:

M. Schalow M. O. Müller

Decision electronically authenticated