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Datasheet for the decision of 19 December 2023

Case Number: T 1779/21 - 3.3.04

Application Number: 14724037.8

Publication Number: 2991637

IPC: A61K31/137, A61K45/06, A61P25/08

Language of the proceedings: EN

Title of invention:
Fenfluramine for use in the treatment of Dravet syndrome

Patent Proprietors:
Katholieke Universiteit Leuven
University Hospital Antwerp

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Dravet syndrome/KATHOLIEKE UNIVERSITEIT LEUVEN

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0001/03, G 0002/21, T 0609/02, T 0754/11, T 0887/14

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Case Number: T 1779/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 December 2023

Appellant: (Opponent)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondents: (Patent Proprietors)	Katholieke Universiteit Leuven K.U. Leuven R&D Waaistraat 6 Box 5105 3000 Leuven (BE) and University Hospital Antwerp Wilrijkstraat 10 2650 Edegem (BE)
Representative:	Leonard, Thomas Charles Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 September 2021 rejecting the opposition filed against European patent No. 2 991 637 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the decision of the opposition division to reject the opposition to European patent No. 2991637 (the patent), entitled "*Fenfluramine for use in the treatment of Dravet syndrome*", which is based on European patent application No. 14724037.8. The latter had been filed as an international application under the PCT, published as WO 2014/177676 (the application).

II. The opposition was based on Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and Article 100(b) and (c) EPC.

III. With its statement of grounds of appeal, the appellant filed document D28.

IV. In their reply to the appeal, the patent proprietors (respondents) relied on the set of claims of the patent as granted.

V. Claim 1 reads as follows.

"A formulation comprising fenfluramine or a pharmaceutically acceptable salt thereof for use in the treatment of Dravet syndrome,
wherein the formulation is for oral administration, and wherein said treatment comprises administration of fenfluramine as a monotherapy, as the sole therapeutic agent."

VI. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VII. At the end of the oral proceedings, which were held by videoconference, the chairwoman announced the board's decision.

VIII. The following documents are referred to in this decision.

D2 B. Ceulemans et al., "*Successful use of fenfluramine as an add-on treatment for Dravet syndrome*", Epilepsia 53(7), 2012, 1131-1139

D4 B. Ceulemans et al., "*Successful use of Fenfluramine as add-on treatment in Dravet syndrome: a two year prospective follow up*", Eur. J. Paediatr. Neurol. 178, 2013, S4, O11-1866

D5 Annex 1 attached to the respondents' response of 25 May 2017

D6 C. Dravet, "*Dravet syndrome history*", Dev. Med. Child. Neurol. 53(Suppl. 2), 2011, 1-6

D7 K. Gentsch et al., "*Fenfluramine Blocks Low-Mg^{2+}-Induced Epileptiform Activity in Rat Entorhinal Cortex*", Epilepsia 41(8), 2000, 925-928

D13 Declaration by Dr Joseph Sullivan, with accompanying CV

D15 Treatment algorithm from C. Dravet and R. Guerrini, "*Dravet Syndrome*", 2011

D20 M. Wolff et al. "*Severe Myoclonic Epilepsy of Infants (Dravet Syndrome): Natural History and*

Neuropsychological Findings", Epilepsia 47(Suppl. 2), 2006, 45-48

D22 J. Aicardi et al., "*Treatment of self-induced photosensitive epilepsy with fenfluramine*", NEJM 313(22), 1985, 1419

D23 J. Aicardi et al., "*Syncopal Attacks Compulsively Self-induced by Valsalva's Maneuver Associated with Typical Absence Seizures*", Arch. Neurol. 45, 1988, 923-925

D24 B. Clemens, "*Dopamine agonist treatment of self-induced pattern-sensitive epilepsy. A case report*", Epilepsy Res. 2, 1988, 340-343

D25 M. Boel and P. Casaer, "*Add-On Therapy of Fenfluramine in Intractable Self-Induced Epilepsy*", Neuropaediatrics 27(4), 1996, 171-173

D26 P. Casaer and M. Boel, "*Fenfluramine as a Potential Antiepileptic Drug*", Epilepsia 43(2), 2002, 205-206

D27 S. Grosso, et al., "*Dexfenfluramine effective in drug-resistant temporal lobe epilepsy*", Neurology 57, 2001, 1139-1140

IX. The appellant's submissions are summarised as follows.

Disclosure (Article 100(b) EPC)

The teaching of the patent was limited to the use of fenfluramine in combination with further active agents. All the documents cited in the patent (sections [0002] to [0004], in the present proceedings: documents D22 to

D26) described the treatment of different forms of epilepsy (not including Dravet syndrome) by combinations of fenfluramine with several further agents. The patent's experimental part was limited to a "*Comparative Example*" that was a summary of prior-art document D2. The patent did not comprise any new data; in particular, it did not comprise any experimental results or any additional teaching regarding the use of fenfluramine in a monotherapy.

A person skilled in the art would have serious doubts about the efficacy of fenfluramine as a monotherapy for Dravet syndrome. The respondents themselves argued extensively that the person skilled in the art "knew" that the treatment of the highly complex Dravet syndrome required a combination therapy involving different agents acting via multiple mechanisms, and that there was an established "bias" against the use of fenfluramine as a monotherapy for Dravet syndrome. In order to provide a clear and complete disclosure within the meaning of Article 100(b) EPC, the information provided by the patent would have had to dispel these doubts.

X. The respondents' submissions are summarised as follows.

Disclosure (Article 100(b) EPC)

The patent proprietors recognised the potential for fenfluramine to have a clinically significant effect when administered as a monotherapy, and indicated a mechanism of action for this effect (see page 7, lines 1 to 5 of the application as filed). This was confirmed by document D2 (see page 1137, right-hand column, last paragraph). In view of the stated mechanism of action, it would have been plausible to the skilled person that

fenfluramine had anti-convulsive effects, and therefore could be used as a monotherapy in the treatment of Dravet syndrome.

The exact scope of the supporting data in the application as filed did not alter the fact that a fenfluramine monotherapy was clearly envisaged by the patent proprietors and was explicitly disclosed in the application as filed as a mode of administration.

Fenfluramine as a monotherapy had subsequently been shown to have a significant clinical effect in the treatment of Dravet syndrome (see document D5).

The skilled person could carry out the invention across the scope of the claims without any undue burden, following the teaching in the patent, since it merely required the administration of a compound that was already known to the skilled person as a treatment of the same disease, albeit in a combination therapy in the prior art.

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

The respondents requested that the appeal be dismissed and that the patent be maintained as granted.

Reasons for the Decision

Disclosure (Article 100(b) EPC)
Decisions G 2/21 and G 1/03

1. Claim 1 is formulated as a purpose-limited product claim according to Article 54(5) EPC.

2. Point 74 of the Reasons of decision G 2/21 (OJ EPO 2023, A85) confirmed the relevant case law that "*a technical effect, which in the case of for example a second medical use claim is usually a therapeutic effect, is a feature of the claim, so that the issue of whether it has been shown that this effect is achieved is a question of sufficiency of disclosure under Article 83 EPC*" and that "*it is necessary that the patent at the date of its filing renders it credible that the known therapeutic agent, i.e. the product, is suitable for the claimed therapeutic application*".

3. It therefore had to be decided whether fenfluramine as a monotherapy, i.e. as the sole therapeutic agent, could be considered suitable for the treatment of Dravet syndrome at the relevant date. As decision G 2/21 further explains, in point 77 of the Reasons: "[i]*n 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 Enlarged Board of Appeal endorsed the conclusions in decision T 609/02 (see G 2/21, point 75 of the Reasons) and decisions T 754/11 and T 887/14 (see point 76 of the Reasons). The expression "*proof of a claimed therapeutic effect*" in point 77 of the Reasons cannot therefore be interpreted as a deviation from the established case law in the context of second medical uses: it does not apply a stricter requirement than the established case law prior to decision G 2/21. Rather, by referring in the same sentence to a particular situation in which "*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*", the Enlarged Board confirmed that means other than experimental data in the application as filed can establish proof of a claimed therapeutic effect.

5. What is required, however, in the absence of experimental evidence, is for the patent or the application as filed to provide some information demonstrating that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent itself (see T 609/02, points 5 to 9 of the Reasons).

6. Decision G 1/03 (OJ EPO 2004, 413) notes in this regard, in point 2.5.3 of the Reasons, that "[w]*hen an application for a patent is filed, the process of making the invention has to be completed. The requirement of sufficiency of disclosure ensures that a patent is only granted if there is a corresponding contribution to the state of the art. Such a contribution is not present as long as the person skilled in the art is not able to carry out the*

invention. Therefore, the decisive date for fulfilling the requirement has to be the date of filing or priority, as the case may be. Deficiencies in this respect cannot be remedied during the proceedings before the EPO."

7. The board concludes that a contribution to the state of the art which enables the skilled person to carry out the invention has to be present in the application as filed.

The teaching of the patent

8. The patent relates to the treatment of Dravet syndrome with fenfluramine. Dravet syndrome is a rare and catastrophic form of intractable epilepsy that begins in infancy. Children with Dravet syndrome are particularly susceptible to episodes of *status epilepticus*. This severe and intractable condition is categorised as a medical emergency requiring immediate medical intervention, typically involving hospitalisation. *Status epilepticus* can be fatal. It can also be associated with cerebral hypoxia, possibly leading to damage to brain tissue.

9. It was undisputed that the only example in the application as filed, "Comparative Example 1", does not relate to fenfluramine monotherapy, but reports administration together with valproate, a known anti-convulsant (see Table 3). This combination treatment resulted in a seizure-free condition in 66.6% of test subjects, and in a slightly improved reduction in seizures (75%) as compared to the reduction in seizures in patients treated with valproate and stiripentol for two months (69.7%).

10. In the absence of experimental data for fenfluramine monotherapy in the application as filed, the board considered whether achieving the claimed therapeutic effect was made credible in the application as filed in another way (see points 3. and 4. above). "*Monotherapy*" is explicitly mentioned in the application as filed on page 8, lines 11 to 13 and in claim 9, in both cases as an alternative to combination therapy. However, this mere statement is not in itself sufficient to provide any "proof" in the sense of decision G 2/21. The application as filed furthermore states that "[f]*enfluramine has been known to inhibit serotonin reuptake and to trigger the release of serotonin in the brain due to disruption of its vesicular storage. However, until the present invention was made, it was not known that fenfluramine's mechanism of action made it suitable for the treatment of Dravet Syndrome*" (see page 7, first paragraph). The board notes that treatment by therapy does not per se necessitate a complete cure of the disease or even the addressing of its cause, but does include the alleviation of symptoms (see also Case Law of the Boards of Appeal, 10th edition 2022, I.B.4.5.1).

Level of proof required

11. Although the skilled person could conclude, from the data in the patent or the application as filed, that fenfluramine in combination with valproate alleviated some symptoms of Dravet syndrome, it was not clear whether this also applied in a monotherapy. In view of the serious nature of the disease, additional circumstances have to be borne in mind when deciding whether "*proof of the therapeutic effect*" is provided in the application as filed. As noted in document D2:

"*Dravet syndrome is a truly catastrophic therapy-resistant epilepsy syndrome, and families faced with this disorder are required to cope with special circumstances*" (see page 1136, left-hand column, penultimate paragraph). Discontinuation of treatment can lead to a greater number of seizures, potentially with adverse effects on mental development (see for example the case reported in document D4, right-hand column, lines 2 to 4 and D20, page 47, right-hand column, second full paragraph). According to several prior-art documents, including reviews authored by Charlotte Dravet, the physician after whom the disease is named, the standard first-line therapy for Dravet syndrome was valproate, a known anticonvulsant (see for example the upper part of the flowchart in D15). Depending on the response of the individual patient, this treatment was supplemented by additional medicaments (e.g. clobazam and stiripentol or topiramate, see the middle part of D15), while maintaining valproate as the basic medicament. Anti-epileptic drugs that target the sodium channel (e.g. carbamazepine, oxcarbazepine, phenytoin, lamotrigine) had to be avoided, because they were known to aggravate the condition - which could be associated with mutations in the sodium channel gene *SCN1A* (see D6, paragraph bridging columns on page 2 and paragraph bridging pages 3 and 4). The expert declaration submitted by the respondents (D13) states in point 13 that "*removal of potentially efficacious compounds from a drug regimen is done with extreme caution and only with a rationale justifying the removal*".

12. In this particular case, namely a very serious disease for which an established, albeit sub-optimal, therapy exists (only 16% of patients remained seizure-free, see D2, Summary) and where a wrong therapy decision could

lead to irreversible damage, the level of proof required has to be at least such that the skilled person has reason to assume that the standard valproate treatment could be discontinued and replaced by fenfluramine without worsening the condition of the patient.

Mechanism of action

13. In the absence of experimental or clinical data in the application as filed that would indicate that a fenfluramine monotherapy had a therapeutic effect, the board further considered whether the application as filed or the prior art established a direct effect by fenfluramine on a metabolic mechanism specifically involved in the disease. The respondents argued that the inhibition of serotonin reuptake and triggering of the release of serotonin in the brain due to disruption of its vesicular storage, as reported in the application as filed (see page 7, first paragraph), was such a metabolic mechanism. The board does not agree, for the following reasons.

14. Document D2, published shortly before the priority date of the patent, refers to earlier *in vitro* studies (D7) which indicate that "*serotonine releasing drugs (like fenfluramine) could have an effect on the epileptic activity*" (see page 1137, right-hand column, first full paragraph). However, D2 concludes that "*although it is known that fenfluramine increases synaptic serotonin concentration, which has potential anticonvulsive effects, it is unclear whether the serotonin effects explain our favorable results*". In summary, at the filing date it was far from established whether the greater number of seizure-free patients with Dravet

syndrome who were treated with fenfluramine as an add-on therapy resulted from increased serotonin levels.

15. Furthermore, and importantly, the skilled person could not derive from the experimental data in the patent or the application as filed whether fenfluramine was able to exert its beneficial effect alone, or whether it was only acting in support of valproate, i.e. potentiating the effect of this established anti-convulsant.

The teaching of the prior art

16. Since "*proof of the therapeutic effect*" is not provided in the application as filed, the board also considered whether the teaching of the prior art provided the skilled person with any indication of a therapeutic effect of fenfluramine as a monotherapy for Dravet syndrome.

17. Most of the documents cited relate to combination treatments (see for example D22 and D24 to D26). It was undisputed that the only prior-art documents which relate to monotherapy with fenfluramine, D23 and D27, concern distantly related epileptic diseases. Document D23 refers to a single case in which fenfluramine was given - as a monotherapy - to treat self-induced apnoeic syncopes and true epileptic absence seizures. The patient "*responded favorably to treatment with fenfluramine hydrochloride, as already reported in cases of compulsively self-induced syncopes*" (see page 923, left-hand column). In document D27, a single patient with temporal lobe epilepsy was treated with fenfluramine monotherapy. The document also refers to experimental data in rats and mice as a possible mechanistic explanation for the effect of fenfluramine (see paragraph bridging pages 1139 and 1140 and

references cited therein). However, the conclusion in document D27 of an "*involvement of serotoninergic circuits in some forms of drug-resistant temporal lobe epilepsy*" limits the teaching concerning fenfluramine to these particular conditions (page 1140, last paragraph).

18. In view of the established use of fenfluramine in combination with other anti-convulsive medicaments, and the very different nature and isolated cases of the two epileptic diseases for which monotherapy with fenfluramine was reported, the skilled person could not draw any conclusions as to the effectiveness of fenfluramine as a monotherapy for Dravet syndrome.

Conclusion

19. From the technical teaching of the application as filed, even taking into account the prior art, it was not credible that fenfluramine achieved a therapeutic effect in Dravet syndrome patients when given as a monotherapy. In line with decision G 2/21, the board does not take the post-published data (document D5) into account (see Reasons, point 77).

20. The claimed invention is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The ground of opposition of Article 100(b) EPC therefore prejudices maintenance of the patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated