

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

JAZZ PHARMACEUTICALS IRELAND LTD. and
JAZZ PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2016-00546
Patent 8,772,306 B1

Before ERICA A. FRANKLIN, SUSAN L. C. MITCHELL, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Amneal Pharmaceuticals LLC (“Petitioner”) filed a Petition (Paper 1, “Pet.”), requesting institution of an *inter partes* review of claims 1–34 of U.S. Patent No 8,772,306 B1 (Ex. 1001, “the ’306 patent”). Jazz Pharmaceuticals Ireland Ltd. and Jazz Pharmaceuticals, Inc. (collectively, “Patent Owner”) timely filed a Preliminary Response (Paper 10, “Prelim. Resp.”). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.”

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine Petitioner has not shown a reasonable likelihood that it would prevail with respect to any of the challenged claims. We, therefore, decline to institute an *inter partes* review of claims 1–34 of the ’306 patent.

A. Related Proceedings

The parties have identified the following related litigation proceedings involving the ’306 patent: *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, No. 2:13-cv-391 (D.N.J.); *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, No. 2:15-cv-1360 (D.N.J.); *Jazz Pharmaceuticals, Inc. v. Wockhardt Bio AG*, No. 2:15-cv-5619 (D.N.J.); and *Jazz Pharmaceuticals, Inc. v. Lupin Ltd.*, No. 2:15-cv-6548 (D.N.J.). Pet. 58–59; Paper 8. The parties have also identified other cases, including *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, No. 2:15-cv-6562 (D.N.J.) and *Jazz Pharmaceuticals, Inc. v. Par Pharmaceutical, Inc.*, No.

2:15-cv-7580 (D.N.J.), concerning a patent related to the '306 patent. Pet. 59; Paper 8.

In addition, the '306 patent was also the subject of petitions for *inter partes* review filed by Ranbaxy Inc. (IPR2016-00024) and Par Pharmaceutical, Inc. (IPR2016-00002). We denied institution in IPR2016-00002. *See Par Pharm., Inc. v. Jazz Pharm. Ireland Ltd.*, Case IPR2016-00002, Decision, Denying Institution of *Inter Partes* Review (Paper 12) (PTAB Apr. 12, 2016). We instituted an *inter partes* review in IPR2016-00024 on limited grounds, but that proceeding was terminated due to settlement before we reached a final decision on the merits. *See Ranbaxy Inc. v. Jazz Pharm., Inc.*, Case IPR2016-00024, Decision, Institution of *Inter Partes* Review (Paper 10) (PTAB Apr. 12, 2016); Order, Termination of the Proceeding (Paper 15) (PTAB May 23, 2016).

B. The '306 Patent (Ex. 1001)

The '306 patent issued on July 8, 2014, and claims a priority date as early as March 1, 2013. *See* Ex. 1001, Title Page. It names Mark Eller as the sole inventor. *Id.*

The '306 patent relates generally to methods for improving the safety and efficacy of the administration of gamma-hydroxybutyrate ("GHB") or a salt thereof to a patient. *Id.*, Abstract. More specifically, the '306 patent is concerned with treating patients suffering from certain disorders such as cataplexy or narcolepsy, who are concomitantly receiving treatment with valproate, with a reduced dose of GHB. *Id.* at 1:15–36. The specification states that valproate can increase or prolong the effects of GHB, resulting in unsafe conditions such as excessive daytime sleepiness. *Id.* at 17:49–62. In

certain embodiments, the reduced amount of GHB ranges from 1% to 50% of the effective dose normally given to the patient. *Id.* at 1:32–36.

C. Illustrative Claims

Petitioner challenges claims 1–34 of the '306 patent. All of the challenged claims are directed to methods of treating certain sleep disorders by orally administering a reduced dosage of GHB to patients who are concomitantly receiving valproate.

Claims 1, 11, 19, 30, and 33 are independent. Independent claim 1 is illustrative, and reproduced below:

1. A method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, or nocturnal myoclonus with gamma-hydroxybutyrate (GHB) or a salt thereof, said method comprising:

orally administering to the patient in need of treatment at least 5% decrease in an effective dosage amount of the GHB or salt thereof when the patient is receiving a concomitant administration of valproate, an acid, salt, or mixture thereof.

Independent claims 11, 19, 30, and 33 also require either administering or recommending a reduced dose of GHB to a patient who is taking valproate. Petitioner treats all independent claims similarly under each ground asserted in the Petition.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of the claims of the '306 patent on the following grounds:

References	Basis	Claims challenged
Xyrem Label, ¹ Hechler, ² Shinka, ³ and Depakote Label, ⁴	§ 103(a)	1–34
Xyrem Label, Hechler, Shinka, Cagnin, ⁵ and Depakote Label	§ 103(a)	1–34
Xyrem Label, Hechler, Shinka, Depakote Label, and Kaufman ⁶	§ 103(a)	6, 17, 27
Xyrem Label, Hechler, Shinka, Depakote Label, Cagnin, and Kaufman	§ 103(a)	6, 17, 27

¹ Jazz Pharm., Inc., *NDA 21-196/S-005, FDA Approved Labeling Text Dated 11/18/05* (2005) (Ex. 1005).

² Viviane Hechler et al., *γ-Hydroxybutyrate Conversion into GABA Induces Displacement of GABA_B Binding That Is Blocked by Valproate and Ethosuximide*, 281 *J. Pharmacology & Experimental Therapeutics* 753 (1997) (Ex. 1006).

³ Toshihiro Shinka et al., *Effect of Valproic Acid on the Urinary Metabolic Profile of a Patient with Succinic Semialdehyde Dehydrogenase Deficiency*, 792 *J. Chromatography* 99 (2003) (Ex. 1007).

⁴ Abbott Labs., *NDA 018723/S-037/S-040/S-043/S-045/S-046, Depakote (Divalproex Sodium) Tablets for Oral Use, FDA Approved Labeling Text Dated October 7, 2011* (2011) (Ex. 1009).

⁵ Annachiara Cagnin et al., *γ-Hydroxybutyric Acid-Induced Psychosis and Seizures*, 21 *Epilepsy & Behav.* 203 (2011) (Ex. 1008).

⁶ Elaine E. Kaufman & Thomas Nelson, *An Overview of γ-Hydroxybutyrate Catabolism: The Role of the Cytosolic NADP⁺-Dependent Oxidoreductase EC 1.1.1.19 and of a Mitochondrial Hydroxyacid-Oxoacid Transhydrogenase in the Initial, Rate-Limiting Step in This Pathway*, 16 *Neurochemical Res.* 965 (1991) (Ex. 1015).

II. DISCUSSION

A. Claim Construction

We interpret claims using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b); *see also* *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings).

We determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case. *See, e.g.,* *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Prior Art Relied Upon

Petitioner relies upon the following prior art in its challenges.

1. *Xyrem Label (Ex. 1005)*

The Xyrem Label discloses the prescribing information for an oral administration of sodium oxybate (i.e., a GHB salt), a central nervous system depressant for treating excessive daytime sleepiness and cataplexy. Ex. 1005, 1, 7. According to the Xyrem Label, the “dose of Xyrem should be titrated to effect.” *Id.* at 22. The Xyrem Label recommends a starting dose of sodium oxybate of 4.5 g/night, divided into two equal doses of 2.25 g. *Id.* at 22–23. The Xyrem Label also recommends increasing the dosage to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose), and further discloses that the effective dose range is 6 to 9 g/night. *Id.* at 23.

The Xyrem Label includes a black box warning on the first page that the drug “[s]hould not be used with alcohol or other CNS depressants.” *Id.* at 1. Additionally, the Xyrem Label indicates that “[s]odium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase [SSADH] deficiency.” *Id.* at 8.

2. *Depakote Label (Ex. 1009)*

The Depakote Label discloses the prescribing information for an oral administration of divalproex sodium (valproate), an anti-epileptic drug for treating seizures, migraine headaches, and bipolar disorder. Ex. 1009, 1. The Depakote Label warns that “[s]ince valproate products may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities.” *Id.* at 48.

3. *Cagnin (Ex. 1008)*

Cagnin is a case report describing a patient affected with bipolar disorder and alcohol dependence who experienced seizures after co-administration of valproate and GHB. Ex. 1008, 203. The patient had been receiving a 500 mg dose of valproate, twice daily, as mood-stabilizing treatment. *Id.* The patient also began receiving a dose of 3500 mg/day of GHB for treatment of alcohol dependence. *Id.* Subsequently, the patient developed psychotic behavior and experienced seizures. *Id.* at 203–04. Cagnin states that “[o]nly GHB discontinuation restored the neurotransmitter balance and caused seizures to cease.” *Id.* at 205.

Cagnin suggests that an interaction between valproate and GHB may have triggered the seizures. *Id.* In particular, Cagnin states that valproate is a potent in vitro inhibitor of SSADH, which “catalyzes the production of

succinate from succinic semialdehyde [SSA], an intermediate product in the metabolic pathway transforming GHB into GABA and vice versa.” *Id.* Cagnin also discloses that “[a]n inherited deficiency of SSADH activity leads to accumulation of [SSA] and, consequently, a 30-fold increase in GHB level and a 2- to 4-fold increase in GABA in the brains of affected rats,” resulting in tonic-clonic seizures and convulsive status epilepticus. *Id.*

4. *Hechler (Ex. 1006)*

Hechler teaches that “GHB is a naturally occurring substance that is located in almost all brain regions, together with succinic semialdehyde reductase, the enzyme responsible for its synthesis.” Ex. 1006, 753 (citation omitted). Hechler discloses that valproate inhibits the metabolism of GHB to SSA by inhibition of GHB dehydrogenase in vivo, which results in an accumulation of GHB in the brain. *Id.* at 754, 757.

5. *Shinka (Ex. 1007)*

Shinka teaches that “[t]he effects of [valproate (“VPA”)] on GHB metabolism have been discussed and it is suspected that the inhibition of SSADH by therapeutic levels of VPA results in enhanced GHB production.” Ex. 1007, 99–100. Shinka further teaches that “GHB is converted to succinic semialdehyde by the reverse reaction with non-specific reductase, and inhibition of this enzyme by VPA is believed to be another reason for accumulation of GHB.” *Id.* at 103–04.

6. *Kaufman (Ex. 1015)*

Kaufman teaches that anticonvulsants, such as valproate, are good inhibitors of GHB dehydrogenase and that, “[i]n addition, GHB dehydrogenase is inhibited by salicylates.” Ex. 1015, 967.

C. Analysis of Petitioner's Patentability Challenges

1. Obviousness of Claims 1–34 Based on the Xyrem Label, the Depakote 2011 Label, Hechler, and Shinka

Petitioner contends that claims 1–34 are obvious based on the combination of the Xyrem Label, the Depakote Label, Hechler, and Shinka. Pet. 22–43. In addition to the teachings of the references, Petitioner relies upon the Declaration of John Horn, Pharm.D., F.C.C.P. Ex. 1003.⁷

With respect to each of the challenged claims 1–34, Petitioner asserts that, a) “[t]he Xyrem Label disclosed a FDA approved GHB formulation for the treatment of narcolepsy and cataplexy” and “that the primary metabolic pathway for GHB involves the enzymes GHB dehydrogenase and SSADH”; b) a skilled artisan “considering drug-drug interactions for GHB would have found Hechler and Shinka relevant as each reference disclosed increases in GHB levels due to inhibited GHB metabolism by valproate”; and c) the skilled artisan “would have considered the Depakote Label for guidance about valproate in assessing drug-drug interactions between GHB and valproate.” Pet. 22–23.

⁷ Petitioner defines the person of ordinary skill in the art (POSA) as someone “hav[ing] at least a bachelor’s degree, master’s degree, Ph.D., Doctor of Pharmacy degree, or medical degree, and at least five years of experience in the field of drug interactions,” with “an understanding of the pharmacokinetics and pharmacodynamics of drugs, and the risks associated with concomitant administration of certain drug combinations.” Pet. 4; Ex. 1003 ¶ 31. Petitioner further asserts that a “POSA could have worked as a part of a multidisciplinary team and utilize his or her own skills, and also take advantage of certain specialized skills of others in the team to solve a given problem.” Pet. 4; Ex. 1003 ¶ 30. We apply that description in our analysis.

Petitioner further asserts that the skilled artisan “would have been motivated to decrease the dose of GHB with concomitant administration of valproate based on the Xyrem Label and Depakote Label” and the understanding “that concomitant administration of valproate and GHB may produce pharmacodynamic and pharmacokinetic drug-drug interactions that could potentially result in enhanced CNS depression and adverse events.” *Id.* at 24–25. Petitioner also asserts that the skilled artisan “would have been further motivated to decrease the administered dose of GHB based on the titration dosing instructions in the Xyrem Label,” which states that the dose of GHB should be “titrated to effect” and discloses a recommended starting dose of 4.5 grams per night that can be increased to a maximum of 9 grams per night in increments of 1.5 grams per night. *Id.* at 27. Petitioner also asserts that the skilled artisan “could have reasonably been motivated to reduce the GHB dose by 50%, as the Xyrem Label discloses that ‘it is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction’ as liver dysfunction will result in increases in GHB in patients.” *Id.* at 28 (citing Ex. 1005, 4, 11). In addition, Petitioner contends that the skilled artisan “would have further understood that routine pharmacokinetic studies could be conducted to identify the specific dosage adjustment needed to safely co-administer GHB and valproate.” *Id.*

Patent Owner argues that a) the prior art’s teachings were inconsistent and contradictory, such that the effects of valproate on GHB in humans would have been unpredictable (Prelim. Resp. 9–22), b) the prior art taught away from co-administration of GHB and valproate (*id.* at 23–28), c) Petitioner failed to show that the skilled artisan would have been motivated to administer reduced GHB doses if valproate caused GHB-related side

effects (*id.* at 28–33), and d) Petitioner fails to show that the skilled artisan would have reasonably expected that the reduced GHB doses would treat the claimed sleep disorders, and do so without resulting side effects (*id.* at 33–39).

We determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to any of the challenged claims. Although the language in each of the independent claims differs somewhat, Petitioner recognizes that each of those claims require the concomitant administration of GHB and valproate, and asserts that the claims would have been obvious for essentially the same reasons. *See* Pet. 29–34. Therefore, our analysis applies to all the challenged claims.

As an initial matter, Petitioner does not sufficiently account for the prior art’s teaching away of the co-administration of GHB and valproate. A reference teaches away from a claimed invention if it “criticize[s], discredit[s], or otherwise discourage[s]” modifying the reference to arrive at the claimed invention. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) (“[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious.”). Here, we find it particularly relevant that Petitioner acknowledges that both Xyrem (GHB) and Depakote (valproate) are CNS depressants that can cause potential drug-drug interactions, but does not otherwise address the explicit black box warning in the Xyrem Label that GHB should not be taken with other CNS depressants. Ex. 1005, 1; Pet. 24–25. Nor does Petitioner address the Xyrem Label’s contraindication of GHB in patients with SSADH deficiency, despite Petitioner’s acknowledgement

that valproate was known to inhibit SSADH activity. Ex. 1005, 8; Pet. 26. Petitioner does not provide any reason why the skilled artisan would have ignored the black box warning and contraindication in the Xyrem Label and co-administer GHB, even at a reduced dose, when valproate is being concomitantly administered to the patient.

Moreover, even if the prior art did not teach away from reducing the effective dosage of GHB by at least 5% when valproate is co-administered, Petitioner has not demonstrated sufficiently that a skilled artisan would have had a reasonable expectation of success in treating the claimed sleep disorders with such a reduced dosage of GHB. Petitioner's reliance upon the Xyrem Label's teaching that GHB doses should be "titrated to effect," which is based on the administration of GHB alone, does not necessarily suggest that a lower dose of GHB could effectively compensate for any increase in endogenous GHB levels caused by valproate administration as discussed in Hechler (Ex. 1006) or Shinka (Ex. 1007) when treating the claimed sleep disorders. Patent Owner points to evidence of record showing that GHB is eliminated from the body through alternate pathways that are not inhibited by valproate, and these alternate elimination pathways may actually decrease GHB levels. Prelim. Resp. 10–13. Petitioner does not account for these other pathways by which GHB may be eliminated. Petitioner, therefore, has not identified a sufficient basis on this record to conclude that any increased brain levels of endogenous GHB caused by valproate could have been predictably compensated for by a corresponding decrease of at least 5% in the amount of GHB orally administered to patients.

Petitioner asserts that "routine pharmacokinetic studies" could be conducted to identify the dosage adjustment needed to safely co-administer

GHB and valproate. Pet. 28. Petitioner, however, does not provide any further explanation or evidence concerning what type of pharmacokinetic studies could be conducted, and why any such studies would have been considered either “routine” or have provided a reasonable expectation of success with a lower dose of GHB concomitantly administered with valproate. *Cf. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (“While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.”).

We, therefore, decline to institute an *inter partes* review based on Petitioner’s first obviousness challenge for any of claims 1–34.

2. *Obviousness of Claims 1–34 Based on the Xyrem Label, the Depakote Label, Hechler, Shinka, and Cagnin*

As a second obviousness challenge, Petitioner contends that claims 1–34 are obvious based on the combination of the Xyrem Label, the Depakote Label, Hechler, Shinka, and the further teachings of Cagnin. Pet. 44–56.

As discussed above, Petitioner has not shown that the combined teachings of the Xyrem Label, the Depakote Label, Hechler, and Shinka render any of the challenged claims obvious. Cagnin does not make up for this deficiency. Petitioner notes that “Cagnin disclosed a case report of a patient who developed psychotic behaviors and tonic-clonic seizures after being administered 3.5 grams of GHB per day concomitantly with valproate” and “suggests that a drug-drug interaction between valproate and GHB may have triggered the seizures.” *Id.* at 46. Petitioner, however, fails

to address the ultimate conclusion in Cagnin that “[o]nly GHB discontinuation restored the neurotransmitter balance and caused seizures to cease.” Ex. 1008, 205. Thus, as with the Xyrem Label, Cagnin appears to teach away from the co-administration of any amount of GHB with valproate.

We, therefore, decline to institute an *inter partes* review based on this obviousness challenge.

3. Obviousness of Claims 6, 17, and 27 Based on the Further Teachings of Kaufman

Petitioner additionally relies upon Kaufman (Ex. 1015) to separately assert that dependent claims 6, 17, and 27 would have been obvious. These claims recite a step of further administering aspirin to the patient. Pet. 56–57. In particular, Petitioner asserts that Kaufman discloses that GHB dehydrogenase is inhibited by salicylates, e.g., aspirin, which could result in increases in GHB levels in vivo, and thus the skilled “would have been further motivated based on Kaufman to decrease the dose of GHB when a patient is concomitantly administered valproate and aspirin.” *Id.* at 57.

Kaufman does not make up for the deficiencies with respect to Petitioner’s reliance on the Xyrem Label, the Depakote Label, Hechler, Shinka, and Cagnin, as discussed above. Accordingly, we decline to institute an *inter partes* review based on the additional obviousness challenges relying upon Kaufman in the combination.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has not demonstrated that the information presented shows that there is a reasonable

likelihood that it would prevail in proving the unpatentability of claims 1–34 of the '306 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), the Petition for *inter partes* review is *denied* as to all challenged claims of the '306 patent.

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