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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

Jazz Pharmaceuticals, Inc. (Jazz) respectfully submits this citizen petition under 21 U.S.C. § 355(q) and 21 C.F.R § 10.30 to request that the Commissioner of Food and Drugs (Commissioner) take the actions set forth below in Section A. Jazz is the sponsor of new drug application (NDA) No. 21196 for Xyrem® (sodium oxybate) oral solution. Jazz petitions out of concern that filers of abbreviated new drug applications (ANDAs) may be seeking approval of generic sodium oxybate products with labeling that differs from that of Xyrem or with risk evaluation and mitigation strategies (REMS) that are not comparable to the Xyrem REMS Program.

Xyrem's labeling identifies a drug-drug interaction (DDI) with divalproex sodium (divalproex) and provides evidence-based dose adjustment and patient monitoring instructions for the concomitant use of both drugs. Recent public court filings indicate that at least one ANDA filer may be trying to "carve out" information regarding divalproex from its product's package insert. Omitting that information would render the generic less safe or effective than Xyrem and, therefore, unapprovable under 21 C.F.R. § 314.127(a)(7).

The Xyrem REMS Program also requires specific risk mitigation actions regarding the divalproex DDI, including prescriber education about the interaction and appropriate dose adjustments, as well as screening of all Xyrem patients for concomitant use with divalproex. A generic sodium oxybate REMS that does not require these risk mitigation steps would not be approvable under 21 U.S.C. § 355-1(i)(1)(B).

A. ACTIONS REQUESTED

Jazz respectfully requests that the Commissioner take the following actions:

1. Refuse to approve any sodium oxybate ANDA that does not include in its proposed labeling the portions of the Xyrem package insert related to divalproex, which are excerpted in Appendix A to this petition; and

2. Refuse to approve any sodium oxybate ANDA that does not include the portions of the Xyrem REMS related to divalproex, which are excerpted in Appendix B to this petition.

B. STATEMENT OF GROUNDS

I. BACKGROUND

A. Xyrem (Sodium Oxybate) Poses Significant Risks Associated With Its CNS Depressant And Sedative Hypnotic Properties.

Xyrem is indicated for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. Xyrem's active ingredient, sodium oxybate, is the sodium salt of gamma-hydroxybutyric acid (GHB), a notorious Schedule I controlled substance and "date rape drug." 21 U.S.C. § 841(g)(2)(A)(i). Xyrem is a Schedule III substance, but non-medical use of Xyrem can lead to penalties under the higher Schedule I controls. *See generally* Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000, Pub. L. No. 106-172, 114 Stat. 7 (Feb. 18, 2000).

Like GHB, sodium oxybate is a sedative-hypnotic that produces dose-dependent central nervous system (CNS) effects. Xyrem's package insert features a boxed warning regarding, among other serious risks, the risk of CNS depression.[1] The Warnings and Precautions section states that "[t]he concurrent use of Xyrem with other CNS depressants . . . may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death"; that Xyrem may impair judgment, thinking, and motor skills; and that "[p]atients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of Xyrem."[2]

Xyrem is also subject to a REMS with elements to assure safe use (ETASU) that were designed, in part, to mitigate risks of CNS depression.[3] Under 21 U.S.C § 355-1(f)(1), REMS with ETASU are reserved for drugs with serious risks that cannot adequately be addressed through labeling alone—those that present risks so severe that they could not be approved, or would have to be withdrawn, absent a REMS with ETASU. Of the more than 3500 reference listed drugs (RLDs) contained in the Orange Book, only about 65 are marketed subject to REMS with ETASU.[4]

ANDA filers have acknowledged the seriousness of the risks addressed in Xyrem's labeling and the Xyrem REMS Program. Par Pharmaceutical, Inc. (Par) stated before the Patent Trial and Appeals Board (PTAB) that "the risk of excessive dosing [of

[1] *See* Xyrem Package Insert (Apr. 2015), http://1.usa.gov/1NCzAQY (Xyrem Package Insert).

[2] *Id.*, § 5.1.

[3] *See* Xyrem REMS Document (June 2015), http://1.usa.gov/1O6jAFj (Xyrem REMS Document).

[4] *Compare* FDA, Orange Book Data Files, http://1.usa.gov/25e043g (visited Sept. 1, 2016) *with* FDA, REMS Data Files and Historic REMS Information, http://1.usa.gov/1qzqWrn (visited Sept. 1, 2016).

sodium oxybate] is high."[5] Amneal Pharmaceuticals LLC acknowledged that increased GHB levels *in vivo* can "lead to adverse events in patients" including daily tonic-clonic seizures and psychotic behaviors.[6] Ranbaxy Inc. agreed that "excess dosing of GHB could lead to adverse effects, including coma or death."[7]

B. A DDI With Divalproex Results In Increased Exposure To Sodium Oxybate And Associated Pharmacodynamic Effects.

Divalproex, also known as valproate, valproic acid, or sodium valproate, is an anticonvulsant drug used to treat a variety of seizure and mood disorders, and to prevent migraines.[8] In 2012, Jazz conducted a clinical evaluation of potential DDI between sodium oxybate and divalproex (the "DDI Study"). In this randomized, double-blind, crossover study, blood and urine samples were taken at predefined times for pharmacokinetic (PK) analysis. Pharmacodynamic (PD) testing during sodium oxybate treatment included the Karolinska Sleepiness Scale and several tests of attention and working memory.[9]

The DDI Study discovered an interaction between sodium oxybate and divalproex resulting in an increase in the plasma level of sodium oxybate when the drugs are co-administered. Specifically, it found a 25% mean increase in systemic exposure to sodium oxybate when co-administered with divalproex, with a 50% or greater increase in exposure observed in some subjects (AUC ratio range up to 1.7). The DDI Study also discovered PD effects resulting from the interaction—the observed increase in sodium oxybate exposure was associated with significantly greater deficits in several tests of attention and working memory.[10] Importantly, these effects were observed using a dose of Xyrem (6 grams) that is well within its recommended dosing range.

The nature of the DDI between sodium oxybate and divalproex was not predictable prior to the DDI Study. The PTAB recently considered this issue when determining

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[5] Petition for *Inter Partes* Review of U.S. Patent No. 8,772,306 at 27, Paper No. 3, Par Pharm., Inc. v. Jazz Pharm., Inc., IPR2016-00002 (P.T.A.B. Apr. 12, 2016) (Par PTAB Petition) (Exhibit 1).

[6] Petition for *Inter Partes* Review of U.S. Patent No. 8,772,306 at 3, 16, Paper No. 1, Amneal Pharm. LLC v. Jazz Pharm., Inc., IPR2016-00546 (P.T.A.B. filed Feb. 2, 2016) (Exhibit 2).

[7] Petition for *Inter Partes* Review of U.S. Patent No. 8,772,306 at 11, Paper No. 1, Ranbaxy Inc. v. Jazz Pharm., Inc., IPR2016-00024 (P.T.A.B. Apr. 12, 2016) (Ranbaxy PTAB Petition) (Exhibit 3).

[8] Depakote® Package Insert, § 1 (Feb. 2016), http://bit.ly/29tjlCO (Depakote Package Insert).

[9] The software used to conduct these tests, the Cognitive Drug Research (CDR) computerized assessment system, has been used to evaluate the safety and adverse event profile of a number of other FDA-approved sedative hypnotics, including Lunesta, Ambien, Edluar, and Zolpimist.

[10] Eller M, Wang Y, Wesnes K, Alvarez-Horine S, Benson B, Black J. Evaluation of drug–drug interactions of sodium oxybate with divalproex: Results from a pharmacokinetic/pharmacodynamic study. *Sleep Medicine*. 2013 December; 14:e302-e303 (Exhibit 4).

not to institute *inter partes* review of the key claims made in Jazz's patents covering the concomitant use of sodium oxybate and divalproex.[11] The PTAB found that, while certain literature may have suggested "that valproate can cause an accumulation of GHB levels in the brain," there also was prior scientific evidence "showing that GHB is eliminated from the body through alternate pathways that are not inhibited by valproate, and these alternative elimination pathways may actually *decrease* GHB levels." In other words, prior to the DDI Study, a practitioner would not have known that co-administering divalproex with sodium oxybate would result in a net increase in overall exposure to sodium oxybate. Nor would a practitioner have had "a reasonable expectation that any increased brain levels of GHB caused by valproate could have been predictably compensated for . . . by simply decreasing . . . the amount of GHB administered to patients." At best, s/he "would have had to conduct further experimentation (e.g., drug-drug interaction studies) to determine the appropriate dose of GHB to treat the claimed sleep disorders when valproate is concomitantly administered."[12] PTAB also found that the dose could not simply be "titrated to effect" to effectively compensate for any increase in endogenous GHB levels caused by valproate co-administration.[13]

C. The DDI Study Results Were Added To The Xyrem Package Insert, Along With Specific Dose Adjustment And Patient Monitoring Instructions Derived From Those Results.

Based on the DDI Study, FDA approved revised labeling for Xyrem in April 2014.[14] As revised, the Clinical Pharmacology section of the Xyrem package insert describes the DDI Study and its findings:

> Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with Xyrem and divalproex sodium . . . . Divalproex sodium: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25%, while Cmax was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment

[11] *See* U.S. Patent Nos. 8,772,306 and 9,050,302 (the '306 and '302 patents).

[12] Decision Instituting (in Part) *Inter Partes* Review at 13, Paper No. 10, Ranbaxy Inc. v. Jazz Pharm., Inc., IPR2016-00024 (P.T.A.B. Apr. 12, 2016) (Ranbaxy PTAB Decision) (Exhibit 5).

[13] Decision Denying *Inter Partes* Review at 12, Paper No. 11, Amneal Pharmaceuticals LLC . v. Jazz Pharm., Inc., IPR2016-00546 (P.T.A.B. July 28, 2016) (Amneal PTAB Decision) (Exhibit 6).

[14] *See* Supplement Approval Letter from Dr. Eric Bastings, Dep. Dir., DNP, CDER to Jazz Pharm., NDA 21196 (Apr. 11, 2014), http://bit.ly/29RIMQJ.

> on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone.[15]

In addition, the Dosage and Administration section instructs how to reduce the dose of Xyrem if a patient is also taking divalproex and instructs prescribers to monitor patient response to the adjusted dosing:

> Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose when introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly.[16]

The Drug Interactions section reiterates that an initial Xyrem dose reduction of at least 20% should be taken if divalproex is prescribed to patients already taking Xyrem, and underscores that prescribers should "closely" monitor the patient's response and make further adjustments if necessary.[17] Similar language also is included in the Highlights of Prescribing Information.[18] FDA publicly announced these changes to the Xyrem labeling in its monthly MedWatch alert regarding important "Safety Labeling Changes."[19]

As discussed above (*see supra* at 3-4), prior to the 2014 changes to the Xyrem package insert, practitioners had no evidence-based method to determine the appropriate dose of Xyrem when co-administered with divalproex. Moreover, the labeling for divalproex does not contain information about the interaction between that drug and sodium oxybate.[20] As a result, Xyrem's labeling is the only FDA-approved source that identifies the DDI between divalproex and sodium oxybate, explains how to adjust the dose of sodium oxybate when the two drugs are co-administered so as to avoid sodium oxybate's side effects while retaining its efficacy, or alerts practitioners to the need to monitor the patient's response when the two drugs are co-administered.

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[15] Xyrem Package Insert, § 12.3.

[16] *Id.*, § 2.4.

[17] *See id.*, § 7.2.

[18] *See id.*, Highlights of Prescribing Information.

[19] FDA, MedWatch Safety Alerts, April 2014 Safety Labeling Changes, http://1.usa.gov/1TstVMw (last updated May 16, 2014).

[20] *See generally* Depakote Package Insert.

D. The Xyrem REMS ETASU Include Aspects To Mitigate The Risks Associated With The Co-Administration Of Divalproex With Sodium Oxybate.

In February 2015, FDA finalized the REMS for Xyrem.[21] The goal of the REMS is to "mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion."[22] Objectives include informing "prescribers, pharmacists, and patients of . . . [t]he risk of significant CNS and respiratory depression associated with Xyrem" and screening "for concomitant use of sedative hypnotics and other potentially interacting agents."[23]

Several aspects of the ETASU in the REMS are designed to mitigate the risks posed by the potential DDI with divalproex. Physicians who wish to prescribe Xyrem must enroll in the Xyrem REMS Program.[24] To enroll, the prescriber must confirm that s/he has read and understands the information in the Prescriber Brochure.[25] That brochure, in turn, instructs how the dose of Xyrem should be adjusted downward if co-administered with divalproex sodium:

> An initial XYREM dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYREM dose when introducing XYREM. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYREM and divalproex sodium is warranted.[26]

In addition, prescribers must screen patients for concomitant medications[27] and list all known medications on the Prescription Form.[28] That form is then transmitted to the Central Pharmacy for review by technical staff and pharmacists, who also must

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[21] *See* Supplement Approval Letter from Dr. Billy Dunn, Dir., DNP, CDER to Jazz Pharm., NDA 21196 (Feb. 27, 2015), http://bit.ly/29XxhKC.

[22] Xyrem REMS Document, § I.

[23] *Id.*, §§ I.A.1, I.B.1.

[24] Xyrem REMS Document, § II.B.1.a; *see also* Xyrem REMS Program Prescriber Enrollment Form (June 2015), http://1.usa.gov/1NCGpC8 (Prescriber Enrollment Form).

[25] Xyrem REMS Document, § II.B.1.a.i; Xyrem REMS Program Prescriber Brochure, p. 6 (June 2015), http://1.usa.gov/1Y1rgwH (Prescriber Brochure).

[26] Prescriber Brochure at 10.

[27] Xyrem REMS Document, § II.B.1.b.ii.d; *see also* Xyrem REMS Program Prescription Form, p.2 (June 2015), http://1.usa.gov/1XMomx8 (Prescription Form).

[28] Xyrem REMS Document, § II.B.1.b.v.

receive mandatory training on the safe use of Xyrem.[29] Part of that training includes use of the Patient Counseling Checklist,[30] which requires the pharmacist to check (twice) whether the patient is taking divalproex.[31] If the answer is "yes and there is not confirmation of prior prescriber knowledge," then the pharmacist must "call the prescriber to consult."[32] This ensures prescriber awareness of the co-administration of two potentially interacting drugs, and it provides the prescriber another opportunity to consider adjusting the dose based on the dose adjustment instructions in the Xyrem package insert and Prescriber Brochure.

Finally, information regarding concomitant medications gathered through the checklist or prescriber interactions must also be documented in the Xyrem REMS Program central database, where it becomes part of the patient information that pharmacists must review prior to dispensing Xyrem.[33]

E. Certain Filers May Attempt To "Carve Out" Information In The Xyrem Package Insert Relating To The Co-Administration of Divalproex And Sodium Oxybate.

As noted above (*see supra* at note 11), Jazz is the owner of the '306 and '302 patents, which relate to the co-administration of sodium oxybate and divalproex. Both are currently listed for Xyrem in the Orange Book with Use Code U-1532, which corresponds to a "method of treating excessive daytime sleepiness and/or cataplexy in narcolepsy patients with sodium oxybate when divalproex sodium is concomitantly administered."[34]

Seven ANDA filers have notified Jazz of Paragraph IV certifications regarding the '306 and '302 patents. One of the seven, Par Pharmaceutical, asserted in its notices that it proposes to market its generic sodium oxybate product without the divalproex DDI information contained in Xyrem's labeling. Specifically, Par informed Jazz that its proposed generic sodium oxybate product:

> "will not include a package insert that instructs a physician, pharmacist, patient, or other person involved in the treatment of the patient to determine

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[29] *Id.*, § II.B.2.a.ii-iii.

[30] *Id.*, § II.B.2.b.i; *see also* Xyrem REMS Program Patient Counseling Checklist (June 2015), http://1.usa.gov/1U5MHXh (Patient Counseling Checklist)

[31] *See* Patient Counseling Checklist at 5, 7.

[32] *Id.* at 7. The Prescriber Brochure alerts prescribers that the central pharmacy will notify them of any potential for drug interactions based on patient counseling. *See* Prescriber Brochure at 9.

[33] Xyrem REMS Document, §§ II.B.2.b.i, iii.

[34] FDA, Orange Book, Patent Use Codes and Definitions, http://bit.ly/2bmhRve (last visited Sept. 1, 2016).

if the patient has taken, or will take, a concomitant dose of valproate, an acid, salt, or mixture thereof";[35]

"will not include a package insert that instructs a physician, pharmacist, patient, or other person involved in the treatment of the patient to warn the patient of a potential drug/drug interaction due to the combination of valproate, an acid, salt, or mixture thereof and the GHB salt";[36]

"will not include a package insert directing a physician, pharmacist, patient, or other person involved in the treatment of the patient to reduce the daily dosage amount of GHB or salt thereof by at least 20% during concomitant administration of divalproex sodium";[37] and

"will not include a package insert directing a physician . . . or other prescriber to monitor patient response to GHB during concomitant administration of divalproex sodium and to adjust the GHB dose."[38]

Although Par's notices disclaimed the intent to seek approval for the use claimed by the '306 and '302 patents, Par cannot lawfully maintain Paragraph IV certifications "with respect to patents that claim a use for the listed drug for which the applicant is not seeking approval."[39] Jazz therefore had no reason to believe that FDA would consider omitting information regarding the divalproex DDI from the labeling for generic sodium oxybate products based on Par's Paragraph IV certifications.

A recent public filing by Par suggests, however, that Par may have asked FDA to consider just such an action. In March 2016, Par moved for a judgment of noninfringement on the '306 and '302 patents and included a "side-by-side comparison" of the labeling for its proposed generic and that of Xyrem.[40] Although that filing was made under seal, public portions of related pleadings, which were filed with the court in late July 2016, suggest that Par has submitted, and believes that FDA may approve, an ANDA with labeling that omits the protected DDI

[35] Letter from Michelle Bonomi-Huvala, Par Pharm., Inc. to Jazz Pharm., Inc., Notice of Paragraph IV Certification, Enclosure, p. 12 (Aug. 5, 2014) (Par Aug. 2014 Paragraph IV Notice) (Exhibit 7).

[36] *Id.* at 14.

[37] Letter from Michelle Bonomi-Huvala, Par Pharm., Inc. to Jazz Pharm., Inc., Notice of Paragraph IV Certification, Enclosure, p. 10 (Sept. 1, 2015) (Par Sept. 2015 Paragraph IV Notice) (Exhibit 8).

[38] *Id*. at 14.

[39] 59 Fed. Reg. 50338, 50347 (Oct. 3, 1994).

[40] Decl. of Bradford C. Frese in Supp. of Mot. for J. on the Pleadings as to U.S. Patent No. 8,772,306 Under Rule 12(c), ¶ 11, ECF No. 244-1, Jazz Pharm., Inc. v. Amneal Pharm. LLC et al., No. 2:13-cv-391 (filed Mar. 23, 2016) (Exhibit 9).

information.[41] Par has also recently stipulated, in a public filing, that it has submitted a Paragraph III certification, stating that it will not seek approval prior to expiration of certain Orange Book-listed patents that do not expire until July 2020.[42]

II. DISCUSSION

A. FDA Should Refuse To Approve Any Sodium Oxybate ANDA That Proposes To Omit Any Of The Labeling Information Included In Appendix A To This Petition.

The labeling for a proposed generic drug may differ from the labeling for the RLD by omitting an "indication or other aspect of labeling protected by patent." 21 C.F.R. § 314.94(a)(8)(iv). To approve such an ANDA, FDA must affirmatively find that the omissions "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R § 314.127(a)(7). The information in Xyrem's package insert regarding the divalproex DDI, including the dose adjustment and monitoring instructions, is covered by the '306 and '302 patents. Generic sodium oxybate products marketed with labeling that omits this patent-protected information would be less safe or effective than Xyrem and, therefore, would not be approvable.

1. Allowing ANDA Labeling To Omit The Information in Appendix A Would Violate 21 C.F.R. § 314.127(a)(7).

As a general rule, safety information contained in the labeling of an RLD should not be omitted from ANDA labeling. Omitting a precaution, warning, or similar information necessarily results in a generic product that is "less safe or effective" in violation of 21 C.F.R. § 314.127(a)(7).

The patent-protected information in Xyrem's labeling is precisely the sort of safety information that cannot lawfully be carved out of generic labeling. Sodium oxybate has a steep dose-response curve and narrow margin of safety, and has been associated with obtundation and clinically significant respiratory depression even when used as directed.[43] The labeling at issue identifies a DDI with divalproex that (a) increases exposure to sodium oxybate; (b) has been associated with PD changes

[41] *See* Jazz's Mem. of Law in Opp'n to Par's Mot. for J. on the Pleadings as to U.S. Patent No. 8,772,306 Under Rule 12(c) (Redacted), ECF No. 308, Jazz Pharm., Inc., v. Amneal Pharm. LLC et al., No. 2:13-cv-391 (filed July 21, 2016) (Exhibit 10); Def. Par's Reply to Jazz's Opp'n to the Mot. for J. on the Pleadings as to U.S. Patent No. 8,772, 306 Under Rule 12(c) (Redacted), ECF No. 309, Jazz Pharm., Inc., v. Amneal Pharm. LLC et al., No. 2:13-cv-391 (filed July 25, 2016) (Exhibit 11).

[42] Letter from Charles M. Lizza to Hon. Esther Salas, U.S.D.J., p. 3 (Enclosure at 1), ECF No. 312, Jazz Pharm., Inc. v. Amneal Pharm. LLC et al., No. 2:13-cv-391 (filed Aug. 12, 2016) (containing proposed Stipulation and Order of Dismissal) (Exhibit 12).

[43] *See* Xyrem Package Insert, Boxed Warning

as shown by decrements in tests of memory and cognition; and (c) was unknown and unpredictable prior to the study that led to its addition to the Xyrem package insert.[44] It also includes specific dose adjustment instructions to safely address this interaction (i.e., to avoid sodium oxybate's side effects while retaining its efficacy), as well as instructions for close patient monitoring.[45]

This information enables informed treatment decisions by prescribers considering co-administration of these two agents. It makes prescribers and patients aware of the specific divalproex-sodium oxybate DDI when they otherwise would not be, and provides dose-adjustment and monitoring instructions they otherwise would not have. Such knowledge is particularly important with respect to patients already on a stable dose of sodium oxybate when divalproex is introduced, given that they will have developed an understanding of how they respond to sodium oxybate, including the potential side effects and sedative-hypnotic properties of the drug. A sudden and unexpected increase in exposure to sodium oxybate from a DDI with divalproex may be dangerous for such patients, because they would not expect or be prepared to deal with an increase in sedation or exacerbated side effects (e.g., the residual effects on mental alertness and motor coordination addressed in the Warnings and Precautions section of the Xyrem labeling).[46] This is particularly true for patients at the high end of the exposure distribution curve, who, as demonstrated by the DDI study, could experience a 50% or greater increase in exposure to sodium oxybate when divalproex is co-administered.[47]

The clinical importance of the protected divalproex DDI information is reflected by its placement in the Xyrem package insert. For instance, the divalproex dose adjustments and monitoring instructions are contained in the Dosage and Administration section. FDA guidance teaches that DDI information is included in that section when it "is essential for prescribing decisions."[48]

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[44] *See supra* Sec. B.I.B, C.

[45] *See supra* Sec. B.I.C.

[46] *See* Expert Report of Leslie Z. Benet, Ph.D. ¶¶ 19-20 (Benet Rept.) (Exhibit 13).

[47] The Agency has emphasized the importance of protecting patients at the high end of the exposure distribution. *See*, *e.g.*, FDA, Draft Guidance, Evaluating Drug Effects on Ability to Operate a Motor Vehicle, p. 8 (Jan. 2015), http://1.usa.gov/22isST9 ("Although analysis of safety endpoints based on mean effect can be informative . . . clinically meaningful impairment in patients at the high end of drug exposure might not be detected by mean changes."); FDA, Approval Package, NDAs 019908 & 021774, p. 87 (Apr. 19, 2013), http://1.usa.gov/1sHrPQK ("The Division is concerned about unsafe zolpidem levels in patients *at the high end of the population distribution*, not average effects.") (emphasis in original).

[48] FDA, Guidance for Industry, Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, p. 5 (Feb. 2013), http://1.usa.gov/1W7BVGv (Labeling Guidance).

Co-administration with divalproex also is discussed twice in the Highlights of Prescribing Information section of the package insert. As explained in the preamble to 21 C.F.R. § 201.57, information included in the Highlights section is "significant to the clinical use of the drug and, therefore, [has] significant clinical implications for practitioners."[49] Put another way, the Highlights section condenses "crucial prescribing information" to which "practitioners most commonly refer and regard as most important."[50]

Omitting the divalproex DDI labeling would leave prescribers to rely solely on the general warning in section 5.1 of the Xyrem package insert about concurrent use of sodium oxybate with other CNS depressants.[51] That general warning, however, contemplates only the potential additive sedative effects of other drugs; it does not make prescribers aware of any potential interaction between sodium oxybate and other drugs.[52] Nor does the general warning inform prescribers of the specific interaction with divalproex, which has been shown to increase exposure to sodium oxybate in some cases by more than 50%, or provide specific instructions on how to manage the potential for increased exposure.[53]

Prescribers relying on section 5.1's general warning in deciding whether and how to co-administer the two drugs would thus assume, incorrectly, that they need only consider the added sedative potential associated with divalproex (without also considering the increase in sodium oxybate exposure resulting from the interaction between the two drugs). Prescribing decisions based on this incorrect assumption would risk increased GHB exposure and associated adverse events, as prescribers would be unlikely to adjust the patient's sodium oxybate dose in a way that takes into account and compensates for the increased exposure to and risk of sedation from sodium oxybate that comes from the divalproex interaction.[54]

Indeed, the general warning in section 5.1 would leave prescribers to guess from among five different treatment options: (1) reducing the dose of sodium oxybate; (2) reducing the dose of divalproex; (3) reducing the dose of both drugs; (4) not prescribing divalproex; or (5) not prescribing sodium oxybate.[55] Only the first would be qualitatively consistent with the instructions in Xyrem's labeling. But even if a prescriber were to select that option, s/he would lack the information in Xyrem's labeling regarding the specific dose reduction to be used, and would not appreciate

[49] 71 Fed. Reg. 3922, 3938 (Jan. 24, 2006).

[50] Labeling Guidance at 6.

[51] Xyrem Package Insert, § 5.1; Benet Rept. ¶ 22.

[52] Benet Rept. ¶¶ 22-23.

[53] *Id*. ¶¶ 24-25.

[54] *Id*. ¶¶ 24-25, 28.

[55] Xyrem Package insert, § 5.1.

that lowering the dose of Xyrem may not result in the intended decrease in the patient's exposure to the drug.

2. Refusing To "Carve Out" The Protected Divalproex Interaction Information And Dose Adjustment Instructions Would Be Consistent With FDA Precedent.

The patent-protected information in Xyrem's package insert regarding the divalproex DDI fits squarely with prior instances where FDA refused to approve proposed omissions of protected labeling.

The situation here mirrors that of Colcrys® (colchicine), where FDA determined that patent-protected labeling regarding DDIs between colchicine and P-gp and strong CYP3A4 inhibitors could not be omitted from the labeling for a proposed generic. FDA determined that the protected information could not be carved out because it included "new, quantitative information about the extent of changes in exposure" related to the DDIs and "relevant dose adjustments needed to prevent unnecessary toxicity."[56]

As in Colcrys, the protected Xyrem labeling includes new, quantitative information about the extent of changes in exposure to sodium oxybate when co-administered with divalproex sodium, and relevant dose adjustments to prevent unnecessary toxicity. If anything, the need to include the protected DDI information is even starker here. The DDIs between colchicine and P-gp and strong CYP3A4 inhibitors were at least generally known in the medical community prior to being included in the Colcrys package insert. As discussed above (*see supra* at 3-4), there was no previous identification in the literature of the nature of the interaction of divalproex and sodium oxybate in humans that would inform dosing.

In the case of Rapamune® (sirolimus), FDA determined that protected labeling was "necessary for prescribing physicians to titrate or individualize the [patient's] therapy," and could not be omitted because it was information "that any physician should receive to appropriately determine treatment for all indications for sirolimus."[57] This is precisely the case here, where Xyrem's protected labeling is necessary for prescribers to titrate or individualize patients' sodium oxybate

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[56] Letter from Janet Woodcock, Director, CDER to Gary L. Veron, Sidley Austin LLP, Docket No. FDA-2010-P-0614-0072, pp. 19-20 (May 25, 2011). FDA later approved a colchicine product with labeling that did not contain the same DDI information as Colcrys. But that product, Mitigare®, was approved pursuant to a 505(b)(2) application, meaning that it was not subject to the statutory "same labeling" requirement. Further, the sponsor of Mitigare conducted new DDI clinical studies with findings different from those reported in the Colcrys labeling. *See* FDA, Summary Review Memorandum, NDA 204820, p.1 (Sept. 26, 2014), http://1.usa.gov/27ZxmC5.

[57] Letter from Steven K. Galson, Acting Director, CDER to Michael S. Labson & Elizabeth M. Walsh, Covington & Burling, Docket No. FDA-2003-P-0002-0003 (formerly Docket No. 2003P-0518/CP1), pp. 3-4 (Sept. 20, 2004).

therapy in the presence of divalproex sodium, which may be co-administered to patients taking Xyrem for any of Xyrem's approved indications.

In a similar vein, FDA struggled for years with a carve-out dilemma regarding statements in the Precautions section of the labeling for Skelaxin® (metaxalone) that taking the drug with food may enhance general CNS depression and that elderly patients may be especially susceptible to this CNS effect. FDA recognized that "[c]arving out patent-protected language from the Precautions section of a label that pertains to a labeled use would generally not be permitted."[58] The rule against carving out warnings or precautions applies here with redoubled force: Xyrem's labeling both identifies an interaction that may enhance CNS depression and provides specific dosing adjustment instructions—something that Skelaxin's protected labeling never did.

B. ANDAs With Proposed REMS That Do Not Require The Same Risk Mitigation Requirements Relating To Co-Administration With Divalproex As The Xyrem REMS Are Unapprovable.

To be approvable, the REMS for any sodium oxybate ANDA product must contain the same or "comparable" aspects with respect to each of the aspects of the Xyrem REMS.[59] Sodium oxybate ANDA filers may try to seek approval with REMS that will not require the risk mitigation actions required under the Xyrem REMS related to the divalproex DDI. These aspects of their REMS ETASU would not be comparable to Xyrem's, which means their ANDAs would not be approvable.

As explained above (*see supra* at 6-7), the ETASU of the Xyrem REMS require education about the interaction between the two drugs and appropriate dose adjustments when they are co-administered; screening for co-administration of divalproex with Xyrem; and that REMS program pharmacists alert prescribers to, and document in the REMS central database for use in future dispensing decisions, information regarding patients who are prescribed both drugs. In contrast, Par has said that it:

> "will not [. . .] instruct[] a physician, pharmacist, patient, or other person involved in the treatment of the patient to determine if the patient has taken,

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[58] Memorandum from Martin Shimer, Branch Chief, Regulatory Support Branch, Office of Generic Drugs to ANDA 040445 re: Background for Sandoz' Metaxalone Tablets, 800mg; Decision regarding non-forfeiture of 180-day exclusivity, p. 7 (Mar. 29, 2010), http://1.usa.gov/1O07W0F (p. 217 of electronic file). FDA never did permit the carve-out, as the question became moot when the patents in question were invalidated. *Id*.

[59] *See* 21 U.S.C. § 355-1(i)(1)(B) (permitting, if certain determinations have been made, waiver of the requirement that an ANDA product use a single, shared system of ETASU with the RLD and instead "permit the [ANDA] applicant to use a different, *comparable* aspect of the" ETASU) (emphasis added).

> or will take, a concomitant dose of valproate, an acid, salt, or mixture thereof";[60] and
>
> "will not [. . .] direct[] a physician, pharmacist, patient, or other person involved in the treatment of the patient to reduce the daily dosage amount of GHB or salt thereof by at least 20% during concomitant administration of divalproex sodium."[61]

In other words, Par has said that it will neither screen Xyrem patients for co-administration with divalproex, nor educate prescribers and pharmacists about appropriate dose adjustment when such co-administration occurs. And a REMS that does not screen for concomitant divalproex use also will be incapable of alerting prescribers about, or entering into the central database, or reviewing in the central database prior to future dispensing decisions, the occurrence of concomitant divalproex use by sodium oxybate patients.[62] Consequently, such a REMS would not be approvable, because its ETASU would lack these critical aspects of Xyrem's ETASU and thus fail the statutory test of comparability.[63]

C. Differing Sodium Oxybate Package Inserts and REMS Would Cause Confusion, Undermine The Safe And Effective Use of Sodium Oxybate, And Undermine ANDA Labeling Policy.

FDA has long noted that "[c]onsistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information."[64] Moreover, such consistency "will assure physicians, health professionals, and consumers that a generic drug is as safe

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[60] Exhibit 7 at 12.

[61] Exhibit 8 at 10.

[62] Jazz is not aware of how ANDA filers like Par have sought to meet their burden of demonstrating comparability of a waived REMS. But, if they exclude these risk mitigation actions from their REMS, they cannot credibly show that their REMS remain comparable to the Xyrem REMS with respect to (1) prescriber and pharmacist knowledge about the divalproex-sodium oxybate DDI and associated dose adjustments; (2) screening of Xyrem patients to identify those for whom divalproex has also been prescribed; (3) prescriber consults to alert Xyrem prescribers when their patients are also taking divalproex; and (4) central database documentation for and review of concomitant divalproex use prior to future dispensing decisions. *See* Benet Rept. ¶¶ 30-32.

[63] Omitting these aspects from an ANDA product's REMS also would render the product less safe or effective than Xyrem—and thus violate the statutory same labeling requirement (see *supra* at 9)—because prescribers operating under such a REMS would be less likely than under the Xyrem REMS to be made aware of (i) the interaction between sodium oxybate and divalproex; (ii) the instructed dose adjustment when the two drugs are co-administered; and (iii) the fact that a given patient is, in fact, taking both drugs concomitantly. Benet Rept. ¶¶ 30-32.

[64] 54 Fed. Reg. 28872, 28881 (July 10, 1989).

and effective as its brand-name counterpart."[65] More recently, in the REMS context, Congress and FDA have sought to consolidate risk management for duplicate products in a single shared REMS "to reduce the burden and possible confusion related to having separate" systems for individual medicines.[66]

Here, differing instructions across sodium oxybate package inserts and REMS would confuse patients, prescribers, pharmacists, and other caregivers. Xyrem would identify the interaction between sodium oxybate and divalproex, include dose adjustment instructions for co-administration, and require education, screening, prescriber consults, central database documentation, and review of that documentation in future dispensing decisions in its REMS. By contrast, ANDA products following Par's proposed approach would lack any information whatsoever about this important drug interaction or its management, fail to screen for, alert prescribers to, document in the central database, or review in future dispensing decisions, the concomitant administration of these two interacting agents.

Anyone subjected to these various contradictory messages and differing REMS requirements would understandably be confused regarding screening and appropriate treatment of patients where co-administration of divalproex and sodium oxybate is otherwise warranted. The lack of consistency on this issue across multiple duplicate products would further call into question whether sodium oxybate ANDA products are "as safe and effective as [their] brand-name counterpart."[67]

III. CONCLUSION

For the reasons discussed above, Jazz respectfully asks that the Commissioner take the actions requested in this petition.

C. ENVIRONMENTAL IMPACT

This petition is categorically exempt from the requirement for an environmental assessment or an impact statement pursuant to 21 C.F.R. §§ 25.30 and 25.31.

D. ECONOMIC IMPACT

Information on the economic impact of this petition will be provided upon request.

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[65] 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992).

[66] Bret S. Stetka & Mitchell Mathis, Navigating the New Clozapine REMS, Medscape, Dec. 4, 2015, at 1, *available at* http://www.medscape.com/viewarticle/855225; 21 U.S.C. § 355-1(i)(1)(B).

[67] 57 Fed. Reg. at 17961.

E. CERTIFICATION

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Pursuant to 21 U.S.C. § 355(q)(1)(H), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: July 28, 2016 (Amneal PTAB decision); July 25, 2016 (filing of redacted Par reply brief in patent litigation); July 21, 2016 (filing of redacted Jazz opposition brief in patent litigation); April 10, 2016 (Ranbaxy PTAB decision); Mar. 23, 2016 (Par motion for judgment of noninfringement in patent litigation); Sep. 1, 2015 (Par Paragraph IV notice); and Aug. 5, 2014 (Par Paragraph IV notice). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Jazz Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

Philip J. Honerkamp
Business Unit Head, Sleep
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304
(650) 496-3777

on behalf of Jazz Pharmaceuticals, Inc.

APPENDIX A

The Xyrem package insert contains the following provisions specifically related to divalproex (relevant language is in quotation marks).

HIGHLIGHTS OF PRESCRIBING INFORMATION, *Dosage and Administration*

"Concomitant use with divalproex sodium: an initial reduction in Xyrem dose of at least 20% is recommended (2.4, 7.2)."

2 DOSAGE AND ADMINISTRATION

2.4 Dose Adjustment with Co-administration of Divalproex Sodium

"Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose with introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly. [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*]."

7 DRUG INTERACTIONS

7.2 Divalproex Sodium

"Concomitant use of Xyrem with divalproex sodium resulted in a 25% mean increase in systemic exposure to Xyrem (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial Xyrem dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem [*see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted."

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics, Drug Interactions Studies

"Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with Xyrem and divalproex sodium"

"Divalproex sodium: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25%, while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone [*see Drug Interactions (7.2)* and *Dosage and Administration (2.4)*]."

APPENDIX B

The Xyrem REMS contains the following provisions specifically related to divalproex (relevant language is in quotation marks).

Xyrem REMS Program Prescriber Brochure, at 10:

"An initial XYREM dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking XYREM. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting XYREM dose when introducing XYREM. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYREM and divalproex sodium is warranted."

Xyrem REMS Program Patient Counseling Checklist, at 5:

", or anti-epileptics such as divalproex sodium (Depakote)"

Xyrem REMS Program Patient Counseling Checklist, at 7:

"□ Divalproex sodium or other valproate drug (e.g., valproic acid)"