FDA U.S. FOOD & DRUG ADMINISTRATION

JAN 17 2017

Philip J. Honerkamp
Business Unit Head, Sleep
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

Re: Docket No. FDA-2016-P-2672

Dear Mr. Honerkamp:

This letter responds to the citizen petition you submitted on behalf of Jazz Pharmaceuticals, Inc. (Jazz), which the Food and Drug Administration (FDA or Agency) received on September 2, 2016 (Petition). Your Petition requests that FDA: (1) refuse to approve any sodium oxybate abbreviated new drug application (ANDA) that does not include in its proposed labeling the portions of the Xyrem package insert related to divalproex sodium and (2) refuse to approve any sodium oxybate ANDA that does not include the portions of the Xyrem risk evaluation and mitigation strategy (REMS) related to divalproex sodium (Petition at 1).

Specifically, your Petition expresses concern that at least one ANDA may be seeking approval of a generic sodium oxybate product with labeling that "carves out" information pertaining to the drug-drug interaction (DDI) with divalproex sodium and related dose reduction instructions, which you state is protected by patent. You assert that omitting such information would "render the generic less safe or effective than Xyrem and, therefore, unapprovable under 21 CFR 314.127(a)(7)" (Petition at 1). You also assert that a REMS omitting such information would not be approvable under 21 U.S.C. 355-1(i)(1)(B) (Id.).

We have carefully considered the issues raised in your Petition and the information you have presented. We have also carefully considered the comments submitted to the docket by Par Pharmaceutical, Inc. on November 15, 2016. For the reasons stated below, your Petition is granted with respect to the labeling "carve out." We do not need to reach the question of whether the drug-drug interaction (DDI) information could have been excluded from the REMS materials.

I. BACKGROUND

A. Xyrem

Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. Sodium oxybate is a sedative-hypnotic that produces dose-dependent central nervous system (CNS) effects. Xyrem was originally approved on July 17, 2002, under new drug application (NDA) 21196. Xyrem's approved prescribing information includes a boxed warning describing, among other serious risks, the risk of CNS depression.

Xyrem is subject to a REMS with elements to assure safe use (ETASU) pursuant to section 505-1 of the

Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1).[1] The REMS is designed to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem by informing prescribers, pharmacists, and patients of the risk of significant central nervous system and respiratory depression associated with Xyrem, the contraindication of use of Xyrem with sedative-hypnotics and alcohol, the potential for abuse, misuse, and overdose associated with Xyrem, and the safe use, handling, and storage of Xyrem. Before a Xyrem prescription can be filled, the REMS requires that pharmacy controls exist that screen for concomitant use of sedative-hypnotics and other potentially interacting agents, monitor for inappropriate prescribing, misuse, abuse, and diversion, and notify prescribers when patients are receiving concomitant contraindicated medications, or there are signs of potential abuse or misuse.

B. DDI With Divalproex Sodium in Labeling

Divalproex sodium[2] is an anticonvulsant drug used to treat a variety of seizure and mood disorders, and to prevent migraines. Drug interaction studies were conducted with Xyrem and divalproex sodium which found that coadministration of Xyrem (6 grams (g) per day as two equal doses of 3 g dosed four hours apart) with divalproex sodium (valproic acid, 1250 milligrams (mg) per day) increased mean systemic exposure to sodium oxybate as shown by the area under the curve or AUC by approximately 25 percent, while the maximum concentration or C_{max} was comparable.[3] A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone.[4]

Based on this information, FDA approved revised labeling for Xyrem in April, 2014. As revised, the DOSAGE AND ADMINISTRATION section provides information on how to reduce the dose of Xyrem if a patient is also taking divalproex sodium 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.[5]

In addition, the DRUG INTERACTIONS section provides that an initial Xyrem dose reduction of at least 20 percent should be taken if divalproex sodium is prescribed to patients already taking Xyrem, and states that prescribers should closely monitor the patient's response and make further adjustments if necessary.[6] Dose adjustment language is also included in the Highlights of Prescribing Information.

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[1] The FDA-approved Xyrem REMS can be found on FDA's Web site at http://www.accessdata.fda.gov/drugsatfda_docs/rems/Xyrem_07-15-2015_REMS_document.pdf.

[2] Divalproex sodium was first approved under the brand name Depakote under NDA 18723.

[3] Subsection 12.3 of the Full Prescribing Information for Xyrem, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021196Orig1s019lbl.pdf.

[4] Id.

[5] Xyrem labeling, §2.4

[6] Id., §7.2

C. DDI With Divalproex and the Xyrem REMS

Xyrem is subject to a REMS with ETASU that includes a goal to "mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion . . . ."[7] The REMS requires, among other things, that physicians who wish to prescribe Xyrem must enroll in the Xyrem REMS Program. To enroll, the prescriber must attest to having read and understood the information in the Prescriber Brochure. Page 20 of the Prescriber Brochure contains the following information regarding 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.

The REMS also requires that pharmacists counsel patients[8] utilizing the Patient Counseling Checklist. This checklist directs the pharmacy to ask whether the patient is taking divalproex sodium. If the answer is yes and there is not confirmation of prior prescriber knowledge, then the pharmacist is instructed to call the prescriber to consult.

D. Labeling "Carve-Outs"

The FDCA requires that an ANDA contain

> Information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers.

(section 505(j)(2)(A)(v) of the Act).

FDA's regulations set forth a non-exhaustive list of examples of permissible differences in labeling that may result because the generic drug product and the reference listed drug (RLD) are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the FD&C Act.

(21 CFR 314.94(a)(8)(iv)).

The regulations at § 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected by patent," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (21 CFR 314.127(a)(7)).

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[7] The FDA-approved Xyrem REMS can be found on FDA's Web site at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=345.

[8] This counseling is provided to new patients, patients who are restarting treatment after not receiving the drug for 6 months or longer, and patients who report any changes in medication and/or medical history.

II. DISCUSSION

For the reasons described below, FDA has concluded that omitting information regarding the DDI with divalproex sodium and the resulting dose reduction instructions from the prescribing information for a sodium oxybate product referencing Xyrem as the RLD would render the drug less safe for the remaining non-protected conditions of use. Therefore, the Agency will not permit an ANDA to "carve out" such information from its labeling. FDA does not need to determine whether the absence of this information would have prevented a REMS from being comparable to the RLD REMS.

A. Labeling

As a general matter, FDA does not agree with the Petition's statement that "[o]mitting a precaution, warning, or similar information *necessarily* results in a generic product that is less safe or effective than the applicable RLD" (Petition at 9; emphasis added). FDA regulations at 21 CFR 314.92(a)(1) explicitly state that a proposed generic drug product may omit certain "conditions of use for which approval cannot be granted *because of exclusivity* or an *existing patent* . . . ." (emphasis added). This and other similar provisions affirm that ANDA applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use.[9] The omission of a precaution, warning, or similar information about a condition of use that is not included in the labeling of a generic product may not render the drug less safe for its remaining approved uses. FDA evaluates proposed labeling carve outs on a case-by-case basis and determines whether the differences would render the generic product less safe or effective than the RLD for all remaining, non-protected conditions of use.

Xyrem is a central nervous system depressant, and its administration, even without concomitant medications, can cause serious adverse events, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Given that coadministration of Xyrem and divalproex sodium was shown to increase mean systemic exposure to sodium oxybate by approximately 25 percent, the information about this interaction and the resulting dosing recommendations are important to prevent an exacerbation of these potentially life-threatening effects. In the absence of the DDI information in the Xyrem labeling subsections 2.4 *(Dose Adjustment with Co-administration of Divalproex Sodium),* 7.2 *(Divalproex Sodium),* and 12.3 *(Pharmacokinetics)* a prescriber would not know that coadministering divalproex sodium with sodium oxybate would result in a net increase in overall exposure to sodium oxybate such that the initial dose of sodium oxybate dose should be reduced by at least 20 percent. If that dose adjustment is not made, the patient could be at increased risk of central nervous system depression, including respiratory depression, which may lead to catastrophic effects, including death.
Subsection 5.1 of the Warnings and Precautions section of the Xyrem labeling discusses in general terms the risks of CNS depression when taking Xyrem with other CNS depressant medications, including sedating anti-epileptic drugs, and makes a general recommendation to consider dose reduction.[10] For all

[9] Section 314.94(a)(8)(iv) more explicitly sets forth a non-exhaustive list of examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers (21 CFR 314.94(a)(8)(iv)).

[10] The general warning reads as follows: "Xyrem is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concurrent use of Xyrem with other CNS depressants, including but not limited to: opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with Xyrem should be considered."

but two of the categories of CNS depressants listed, no data exist to characterize the precise interaction with sodium oxybate. By contrast, the study conducted by the Petitioner provided data to characterize the risk associated with the DDI with divalproex sodium, and provided specific dose adjustment recommendations. Unlike the general statement in subsection 5.1, the specific references to divalproex sodium in subsections 2.4, 7.2, and 12.3 provide explicit information regarding the nature and extent of the interaction, the potential effects, and specific recommendations regarding dose reduction. Omitting these references in sections 2.4, 7.2, and 12.3 would render a proposed drug product referencing Xyrem as the RLD less safe for the remaining non-protected conditions of use.

B. REMS

You also request that FDA refuse to approve any sodium oxybate ANDA that does not include the portions of the Xyrem REMS materials related to divalproex sodium. Today, FDA is approving an ANDA for sodium oxybate. The REMS for this ANDA includes a prescriber brochure and patient counseling checklist with the same information about the DDI with divalproex sodium as are contained in the Xyrem REMS materials. Therefore, FDA does not need to determine whether the absence of this information would have prevented a REMS from being comparable to the RLD REMS under section 505-1(i)(1)(B) of the FD&C Act.

III. CONCLUSION

For the reasons discussed above, your Petition is granted with respect to the labeling carve out. FDA will not approve any sodium oxybate ANDA referencing Xyrem as the RLD that does not include in its labeling the portions of the currently approved Xyrem package insert related to the DDI with divalproex sodium, consistent with this response. We need not reach the question of whether the absence of this information in REMS materials would have prevented a REMS from being comparable to the RLD REMS under section 505-1(i)(1)(B) of the FD&C Act.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research