NDA 212690

NDA APPROVAL

Jazz Pharmaceuticals, Inc.
Attention: Arthur Merlin d'Estreux
Director, Global Regulatory Lead
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Dear Mr. d'Estreux:

Please refer to your New Drug Application (NDA) dated January 21, 2020, received January 21, 2020, and your amendments, submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution.

This new drug application provides for the use of Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL, for treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling, unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 19, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212690**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Xywav was not referred to an FDA advisory committee because there were no issues with this application that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate [gamma-hydroxybutyrate]) to ensure the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate [gamma-hydroxybutyrate]) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions.

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require: pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on January 21, 2020, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Xywav will be subject to a REMS with Xyrem (NDA 021196) approved on July 21, 2020. Consequently, Xywav will be subject to the same REMS assessment plan as Xyrem, and will align with subsequent REMS assessments. The REMS will be known as the Xywav and Xyrem REMS.

Your REMS must be fully operational before you introduce Xywav into interstate commerce.

The XYWAV and XYREM REMS Assessment Plan must include, but is not limited to, the following information:

Program Implementation and Operations

1. REMS Program Implementation (1st assessment after approval only)
   a. Date of first commercial distribution of XYWAV
   b. Date when the XYWAV and XYREM REMS website became live and fully operational
   c. Date when the REMS Call Center was operationalized to include both XYWAV and XYREM.

2. REMS Enrollment Statistics (per reporting period and cumulatively)
   a. Patients:
      i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender
      ii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and gender
      iii. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM. Include demographics of discontinued patients and reasons for discontinuation.
      iv. Number and percentage of patients who transitioned from XYREM to XYWAV
      v. Number and percentage of patients who transitioned from XYWAV to XYREM.

   b. Healthcare Providers:
      i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
      ii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)

iii. Number of patients by current enrolled prescriber.

c. Certified Pharmacy
   i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.

3. Utilization Data (per reporting period and cumulatively)
   a. Number and percentage of XYREM prescriptions (new and refills) dispensed
   b. Number and percentage of XYWAV prescriptions (new and refills) dispensed
   c. Number and percentage of XYREM bottles and shipments sent
   d. Number and percentage of XYWAV bottles and shipments sent.

4. REMS Program Operation and Performance Data (per reporting period and cumulatively)
   a. REMS Program Central Database Report
      i. Number and percentage of contacts by stakeholder type (e.g. patients, healthcare providers, pharmacy, other)
      ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (authorized representative, patient, healthcare provider, other)
      iii. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
      iv. Summary of frequently asked questions by stakeholder type and topic
      v. Summary of any REMS-related problems identified and a description of any corrective actions taken
      vi. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
      vii. Summary of program or system problems and a description of any corrective actions taken.

5. REMS Program Compliance (per reporting period and cumulatively)
   a. Audits: Summary of audit activities including but not limited to:
      i. A copy of the audit plan for each audited stakeholder.
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies. The status to include completion status.
      v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
      vii. Confirm documentation of completion of training for relevant staff
      viii. Review of accumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
      ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements.

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