NDA 212690/S-006
NDA 021196/S-036

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals Ireland Limited
Attention: Arthur Merlin d'Estreux, M.Sc.
Director, Global Regulatory Lead – Neurosciences
One Commerce Square
2005 Market Street
Philadelphia, PA 19103

Dear Mr. d'Estreux:

Please refer to your supplemental new drug applications (sNDAs) dated February 12, 2021, received February 12, 2021, 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 and NDA 21196 Xyrem (sodium oxybate) oral solution.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 26, 2021.

The Prior Approval supplemental new drug application 212690/S-006 provides for the new indication of Idiopathic Hypersomnia (IH) for XYWAV. NDA 212690/S-006 and NDA 021196/S-036 provide for modifications to the approved XYWAV and XYREM risk evaluation and mitigation strategy (REMS) to align with the revisions to the XYWAV prescribing information.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA (NDA 212690), including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for XYREM was originally approved on February 27, 2015, and the REMS for XYWAV was approved on July 21, 2020. The two drugs are subject to the same REMS, known as the XYWAV and XYREM REMS. The most recent REMS modification was approved on February 11, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- Changes to the REMS materials to align with the new indication of Idiopathic Hypersomnia for XYWAV
- Changes to the REMS assessment timetable

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

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- Change of the reporting interval for the Knowledge, Attitude, and Behavior Surveys from annually to every other year.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to ensure the benefits of the drug outweigh the risks:

- Changes to the ***Patient Counseling Checklist*** to capture additional information regarding concomitant medication and alcohol use.

Your proposed modified REMS, submitted on February 12, 2021, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS has been revised. Jazz Pharmaceuticals must submit a REMS Assessment on April 26, 2022, and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. 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), indication, 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)

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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.

2. 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.

3. 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.

4. 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

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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 findingsA summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements.

b. A summary report of noncompliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
    i. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
    ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
        1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
        2) The source of the noncompliance data
        3) The results of root cause analysis
        4) What action(s) were taken in response.
c. Healthcare Providers
    i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
    ii. Number of disenrolled prescribers who were associated with a XYWAV and XYREM prescription and number of disenrolled prescribers associated with a XYWAV and XYREM shipment

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