CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**212690 (0001)**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Drug:	**JZP-258***
Proposed Indication:	**Narcolepsy**
Material Submitted:	**New Drug Application**
Correspondence Date:	**1/21/20**
Date Received By Reviewer:	**1/21/20**
Date Review Completed	**7/21/20**
Reviewer:	**Ranjit B. Mani, M.D.**

*The original full name for this product is JZP-258 (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate), oral solution, 0.5 g/mL. Further, the brand name XYWAV (Xywav) has been assigned this product.

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Executive Summary

Recommendation

I recommend that JZP-258 be approved for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

Proposed Indications

This New Drug Application (NDA) seeks the approval of JZP-258 for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

Background To Application

JZP-258 is an aqueous oral solution of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate, 0.5 g/mL (total salt concentration), equivalent to 0.413 g/mL of oxybate, the active moiety. JZP-258 has been developed as a lower-sodium alternative to Xyrem® (sodium oxybate oral solution [500 mg/mL]), which is notable for its high sodium content.

Xyrem® is currently approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years or older with narcolepsy. Xyrem® is available only through a Risk Evaluation and Mitigation Strategy (REMS).

The proposed proprietary name for JZP-258 is XYWAV (Xywav).

Clinical Studies Of JZP-258

- A main clinical efficacy and safety study (Study 15-006).

- Two clinical pharmacology studies (Studies 13-010 and JZP258-010)
- A study investigating the taste of JZP-258 (Study 15-00#

All clinical studies of JZP-258 have been conducted in adults.

Summary of Main Clinical Study Supporting This Application

Study 15-006 is the main clinical study supporting this NDA. Key aspects of this study are summarized below.

Study Design

Protocol 15-006 had the following main features:

- The primary objective of the study was to evaluate the efficacy of JZP-258 in the treatment of cataplexy in patients with narcolepsy. A key secondary objective was to evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness in patients with narcolepsy.
- This was a double-blind, placebo-controlled, randomized withdrawal multicenter study of the efficacy and safety of JZP-258. Patients enrolled in the study included those whose prior treatment status was in any of the following categories:

    1. Treatment with a stable dose of Xyrem® alone for at least 2 months prior to screening.
    2. Treatment with a stable dose of Xyrem® and an unapproved anti-cataplectic for at least 2 months prior to screening.
    3. Treatment with an unapproved anti-cataplectic, but no treatment with Xyrem®.
    4. No prior treatment with Xyrem® or an unapproved anti-cataplectic.

- The study consisted of the following consecutive periods: screening; open-label titration and treatment optimization (of variable duration up to a maximum of 12 weeks, depending on prior treatment status); open-label stable dose treatment (2 weeks); double-blind randomized withdrawal (2 weeks); and safety follow-up (2 weeks). All study patients (i.e., patients in all 4 entry categories) were to be titrated (during the variable-duration open-label titration period) to a dose of JZP-258 that was deemed both effective and tolerable and was maintained for at least 2 weeks prior to entering the two-week open-label stable-dose period.
- A total of about 185 patients were planned to be enrolled in the study, of whom about 130 patients were expected to enter the double-blind

withdrawal period during which they were to be randomly assigned 1:1 to either continuing the same dose of JZP-258 taken during the stable dose period or to placebo.

- The main inclusion criteria for this study were as follows: men and women, aged 18 to 70 years; a primary diagnosis of narcolepsy with cataplexy that met the ICSD–3 criteria or DSM-5 criteria; a history of having at least 14 cataplexy attacks in a typical two-week period and clinically significant symptoms of excessive daytime sleepiness prior to any narcolepsy treatment; treatment status prior to study entry consisting of one of the aforementioned 4 categories; if currently treated with Xyrem, must have had documented improvement documented clinical improvement of cataplexy and excessive daytime sleepiness; and if treated with a stimulant for narcolepsy must have been at an unchanged dose for at least 2 months prior to dosing or must not have been treated at all with a stimulant.

- The primary efficacy parameter was the change in weekly number of cataplexy attacks from the 2-week stable-dose period to the 2-week double-blind treatment period. The key secondary efficacy parameter was the change in Epworth Sleepiness Scale score from the end of the 2-week stable-dose period to the end of the 2-week double-blind randomized-withdrawal treatment period. A number of other efficacy endpoints were also under evaluation in this study, including the Patient Global Impression of Change for narcolepsy overall; the Clinical Global Impression of Change for narcolepsy overall; the change in quality of life based on the Short Form-36 score; and EuroQol 5 Dimensions Self-Report Questionnaire.

- Safety measures were to include adverse events, vital signs, weight, physical examinations, 12-lead electrocardiograms, safety laboratory tests (hematology, clinical chemistry, and urinalysis), and the Columbia-Suicide Severity Rating Scale (for assessing suicidality).

- The final analysis of the primary efficacy parameter and key secondary efficacy parameters was to employ a fixed sequential testing strategy in which the initial step was to involve a comparison of JZP-258 with placebo for the primary efficacy parameter; if the initial comparison was statistically significant (currently $p \leq 0.05$), the treatment groups would then be compared on the key secondary efficacy parameter at the same level of statistical significance (currently $p \leq 0.05$). An analysis of covariance model was to be used at both steps.

- The main study was to be followed by an open-label extension study (phase) lasting 24 weeks.

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