CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

220860Orig1s000

Trade Name:	**ORZEYFUL tablets, 0.5 mg, 1 mg, 2 mg**
Generic or Proper Name:	**(oveporexton)**
Sponsor:	**Takeda Pharmaceuticals U.S.A., Inc.**
Approval Date:	**August 5, 2026**
Indication:	**ORZEYFUL is an orexin receptor 2 (OX2R) agonist indicated for the treatment of narcolepsy type 1 in adult patients.**

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220860Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 220860

NDA APPROVAL

Takeda Pharmaceuticals USA, Inc.
Attention: Mark Swarz
Senior Director, Global Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Mark Swarz:

Please refer to your new drug application (NDA) received December 10, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Orzeyful (oveporexton) tablets.

This NDA provides for the use of Orzeyful (oveporexton) tablets for the treatment of narcolepsy type 1 (narcolepsy with cataplexy) in adult patients.

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.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of Orzeyful under the Controlled Substances Act (CSA). The scheduling of this product in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for Orzeyful shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of oveporexton.

We note that, when the drug is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information and carton and container labeling by submitting a supplement to your NDA. This would include the statements in the labeling detailing the scheduling of oveporexton, as the scheduled substance in Orzeyful, as required under 21 CFR 201.57(a)(2) and (c)(10)(i). Therefore, Orzeyful may be marketed only after DEA has published the notice in the Federal Register announcing the interim final scheduling of oveporexton and you submit a supplement to

your NDA to revise all applicable drug labeling to reflect the drug scheduling described in the notice. For changes to the Prescribing Information, and carton and container labeling to describe the scheduling of Orzeyful, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights of Prescribing Information for DRUG PRODUCT described in 21 CFR 314.70(b)(2)(v)(C).

We note that Orzeyful will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of oveporexton .

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 (Prescribing Information) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to guidance for industry, *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 220860**." Approval of this submission by FDA is not required before the labeling is used.

[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.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Orzeyful (oveporexton) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

ADVISORY COMMITTEE

Your application for Orzeyful was not referred to an FDA advisory committee because the evaluation of the data (when used in the treatment of narcolepsy type 1) did not raise significant or unexpected safety or efficacy issues for a drug of this class or in the intended population. The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease. In addition, outside expertise was not necessary; overall, there were no controversial issues 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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FD&C Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FD&C Act will not be sufficient to identify an unexpected serious risk associated with exposure to oveporexton during pregnancy and lactation.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FD&C Act will also not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

5020-1 Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to oveporexton during pregnancy compared to appropriate comparator population(s).

The timetable you submitted on July 21, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2027
Final Protocol Submission:	02/2028
Interim Report Submission/Other:	04/2029
	04/2030
	04/2031
	04/2032
	04/2033
	04/2034
	04/2035
	04/2036
	04/2037
Study Completion:	04/2038
Final Report Submission:	04/2039

5020-2 Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to drug name regardless of indication during pregnancy with unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry should identify and record pregnancy complications, major and minor congenital malformations, pregnancy complications, spontaneous abortion, stillbirths, elective pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects

on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on July 21, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2027
Study Completion:	08/2037
Interim Report Submission/Other:	08/2028
	08/2029
	08/2030
	08/2031
	08/2032
	08/2033
	08/2034
	08/2035
	08/2036
Final Report Submission:	02/2038

5020-3 Conduct a lactation study to measure concentrations of oveporexton and its major metabolites in breast milk using a validated assay. A mother-infant pair study is recommended. Assess the effects on the breastfed infant, if available, based on study population.

The timetable you submitted on July 21, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2027
Final Protocol Submission:	08/2027
Study Completion:	08/2029
Interim Report Submission/Other:	N/A
Final Report Submission:	02/2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of lower or higher drug exposure in patients with severe hepatic impairment.
Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

5020-4 Evaluate the effect of severe hepatic impairment on safety and pharmacokinetics of oveporexton.

The timetable you submitted on July 21, 2026 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2026
Final Protocol Submission:	06/2027
Study Completion:	10/2028
Final Report Submission:	12/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the requested clinical protocol(s) to your IND 154232 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FD&C Act requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FD&C Act, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

[3] See the guidance for Industry, *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

or clinical trials required under 505(o) on the date required will be considered a violation of FD&C Act section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see guidance for industry, *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, contact the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website.[6]

If you have any questions, contact Tiffanie Taylor, Senior Regulatory Project Manager, at Tiffanie.Taylor@fda.hhs.gov or 301-796-4395.

Sincerely,

{See appended electronic signature page}

Bernard Fischer, MD
Deputy Director
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

[6] https://www.uspnf.com/

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
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