



NDA 212839

NDA APPROVAL

SK Life Science, Inc.
Attention: Darshan Patel
Head, Global Regulatory Affairs
461 From Road, 5th Floor
Paramus, NJ 07652

Dear Mr. Patel:

Please refer to your new drug application (NDA) dated and received November 21, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xcopri (cenobamate) 12.5, 25, 50, 100, 150, and 200 mg tablets.

This NDA provides for the use of Xcopri (cenobamate) tablets for the treatment of partial-onset seizures in adult patients.

APPROVAL & LABELING

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

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of Xcopri 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 effective date of approval for Xcopri shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of cenobamate.

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

Xcopri, 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 the Highlights of Prescribing Information for Xcopri described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

We note that Xcopri 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 cenobamate.

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 Patient Package Insert and Medication Guide) 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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on November 20, 2019, 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 212839.**” 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>.

ADVISORY COMMITTEE

Your application for Xcopri was not referred to an FDA advisory committee because the clinical trial design was acceptable. The efficacy findings were clear, and the safety profile was acceptable for the intended population.

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.

We are waiving the pediatric study requirement for children less than one month old because necessary studies are impossible or highly impracticable due to difficulties in diagnostic certainty in this age group and a small number of available subjects.

We are deferring submission of your pediatric studies for ages one month to less than 18 years old for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

3712-1 An embryofetal development study of cenobamate in rat.

Final Protocol Submission: 09/2020

Study Completion: 05/2021

Final Report Submission: 11/2021

3712-2 Develop an age appropriate formulation of cenobamate that can be used in children 1 month to less than 2 years old.

Final Report Submission: 01/2021

3712-3 Evaluate bioavailability of the age appropriate formulation for children 1 month to less than 2 years old relative to the approved tablet formulation.

Draft Protocol Submission: 06/2020
Final Protocol Submission: 09/2020
Study Completion: 07/2021
Final Report Submission: 11/2021

3712-4 A study to evaluate the pharmacokinetics, safety, and tolerability of an age-appropriate formulation of cenobamate in children ages 1 month to less than 2 years with partial-onset seizures. This study should identify doses to be used in the efficacy and long-term extension studies for children 1 month to less than 2 years of age.

Draft Protocol Submission: 07/2021
Final Protocol Submission: 11/2021
Study Completion: 04/2025
Interim Report Submission: 04/2026
Final Report Submission: 12/2030

The interim report should provide for the final study analysis to allow for consideration of dosing requirements in the efficacy and safety studies for children 1 month to less than 2 years of age.

3712-5 A prospective, randomized, controlled, double-blinded, efficacy and safety study of cenobamate for the treatment of partial-onset seizures in children from 1 month to less than 2 years of age. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon video/electroencephalographic data. The placebo and drug treatment groups will be compared by inferential statistical methods to identify a treatment effect.

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Study Completion: 12/2028
Final Report Submission: 12/2030

3712-6 Long-term safety study of cenobamate in the treatment of partial-onset seizures in children from 1 month to 2 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included.

Draft Protocol Submission: 07/2021
Final Protocol Submission: 11/2021
Study Completion: 12/2029
Final Report Submission: 12/2030

3712-7 A study to evaluate the pharmacokinetics, safety, and tolerability of an age appropriate formulation of cenobamate to determine a dosing regimen as therapy for partial-onset seizures in children ages 2 years to 17 years of age that provides drug exposure that is similar to the exposure that is effective in adult patients with partial-onset seizures. This analysis will require pharmacokinetic data from studies of both the adult and pediatric patients.

Draft Protocol Submission:	07/2020
Final Protocol Submission:	11/2020
Study Completion:	05/2022
Interim Report Submission:	03/2023
Final Report Submission:	11/2025

The interim report should provide for the final study analysis to allow for consideration of dosing requirements in the efficacy and safety studies for children 2 years to 17 years of age.

3712-8 The efficacy of cenobamate in children ages 2 years to 17 years of age for the treatment of partial-onset seizures will be addressed by a report demonstrating matched exposure to that in adults supporting pediatric extrapolation.

Study Completion:	05/2024
Final Report Submission:	11/2025

3712-9 An open-label long term safety and tolerability study of cenobamate in children ages 2 years to 17 years of age.

Draft Protocol Submission:	07/2020
Final Protocol Submission:	11/2020
Study Completion:	11/2024
Final Report Submission:	11/2025

Submit the protocols to your IND 76809, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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 FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, or infant outcomes resulting from the use of Xcopri during pregnancy or an unexpected risk of adverse outcomes caused by blockade of the cardiac sodium channel.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will 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:

- 3712-10 Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Xcopri (cenobamate) during pregnancy compared to an unexposed control population.

The timetable you submitted on November 11, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2020
Final Protocol Submission:	07/2021
Annual Interim Report Submissions:	07/2022
	07/2023
	07/2024
	07/2025
	07/2026
	07/2027
	07/2028
	07/2029
	07/2030
Study Completion:	07/2031
Final Report Submission:	07/2032

3712-11 Perform additional nonclinical experiments to characterize the effects of cenobamate on the cardiac sodium channel, which should allow for determining the anti-arrhythmic sub-class of cenobamate (i.e., Ia, Ib, or Ic).

The timetable you submitted on November 19, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2020
Final Protocol Submission:	06/2020
Study Completion:	03/2021
Final Report Submission:	06/2021

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk resulting from altered pharmacokinetics of Xcopri due to hepatic impairment.

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

3712-12 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Xcopri (cenobamate) to minimize toxicity in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".

The timetable you submitted on November 7, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Trial Completion:	09/2021
Final Report Submission:	03/2022

Submit clinical protocols to your IND 76809 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 protocols 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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in patients exposed to Xcopri. Submit individual reports as expedited reports to your NDA and directly to the Division of Neurology 2. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with information about dose and dose titration, duration of Xcopri therapy, time of event in relation to duration of therapy, concomitant therapies, treatment given for the event, and outcome. We suggest collecting and storing DNA from patients who have had DRESS after exposure to Xcopri in order to further characterize possible genomic predictors.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

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 For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

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).

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁷

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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, call the Regulatory Project Manager for this application.

If you have any questions, contact LaShawn Dianat, PharmD, Regulatory Project Manager, by email at lashawn.dianat@fda.hhs.gov or by phone at (240) 402-7713.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director (acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
- Carton and Container Labeling

⁷ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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/

WILLIAM H Dunn
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