NDA 212728/S-006

SUPPLEMENT APPROVAL

Biohaven Pharmaceuticals
Attention: Marianne Frost
234 Church Street, Suite 304
New Haven, CT 06510

Dear Ms. Frost:

Please refer to your supplemental new drug application (sNDA) dated and received July 28, 2020, and your amendments, submitted under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDCA) for Nurtec ODT (rimegepant) orally disintegrating tablets.

This Prior Approval sNDA provides for the preventive treatment of episodic migraine in adults.

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.

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, Patient Package Insert), 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.

[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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, 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).

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 studies requirement for children 0 to 5 years of age because necessary studies are impossible or highly impracticable. This is because very few children of this age can be definitively diagnosed with migraine and even fewer would be candidates for preventive therapy.

We are deferring submission of your pediatric studies for children 6 to 17 years of age 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)(4)(C) of the FDCA. These required studies are listed below.

4075-1 An open-label, single-dose study to evaluate the safety, tolerability, and single-dose pharmacokinetics (PK) of rimegepant in patients with migraine age 6 to less than 12 years of age.

Study Completion:	12/2022
Final Report Submission:	04/2028

4075-2 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of episodic migraine in children ages 6 through 17 years. This efficacy study must be designed to show superiority of rimegepant over placebo and is to be submitted as a special protocol assessment (SPA).

Final Protocol Submission:	09/2021
Study Completion:	10/2026
Final Report Submission:	04/2028

4075-3 A pediatric open-label safety study under PREA to evaluate the long-term safety of the preventive treatment of episodic migraine in patients ages 6 through 17 years. This study should be a minimum of 1-year in length.

Final Protocol Submission:	09/2021
Study Completion:	10/2027
Final Report Submission:	04/2028

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 protocol(s) to your IND 109886, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4075-4 Conduct a randomized, double-blind, placebo-controlled trial of Nurtec ODT to evaluate the efficacy of additional dosing regimens for the preventive treatment of episodic migraine. Patients should be randomized 1:1:1 to the approved dosing regimen (Nurtec ODT 75 mg every other day), more frequent dosing of Nurtec ODT 75 mg (based on the available pharmacokinetic data), or placebo. The primary efficacy endpoint will be the change from baseline in mean number of monthly migraine days during weeks 9 through 12. The study duration will be at least 3 months.

[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.

The timetable you submitted on April 13, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission,:	07/2021
Final Protocol Submission:	11/2021
Trial Completion:	01/2023
Final Report Submission:	03/2024

4075-5 Conduct an open-label long term safety trial lasting an additional 3 months after the controlled trial (PMC 4075-4) in at least 300 patients exposed to the more frequent dosing regimen.

The timetable you submitted on April 13, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission,:	07/2021
Final Protocol Submission:	11/2021
Trial Completion:	09/2023
Final Report Submission:	03/2024

Submit clinical protocols to your IND 109886 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for cardiovascular events, hypertensive events, cerebrovascular events, and serious gastrointestinal events after exposure to Nurtec ODT. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSUR)]. Include analyses of the events by age and gender. 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 extent of exposure to Nurtec ODT and most recent exposure to Nurtec ODT, concomitant therapies, treatment given for the event, and outcome. Include a comparison to background rates expected in a migraine population of the same age and gender.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

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