



NDA 215383

NDA APPROVAL

Merck Sharp & Dohme Corporation
Attention: Yuan Xue, PhD
Director, Global Regulatory Affairs
One Merck Dr., PO Box 100
Whitehouse Station, NJ 08889

Dear Dr. Xue:

Please refer to your new drug application (NDA) dated January 15, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Welireg (belzutifan) tablets.

This NDA provides for the use of Welireg (belzutifan) tablets for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

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 Food and Drug Administration (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 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.

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>.

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 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 215383.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Welireg (belzutifan) 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 between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Welireg was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

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(ies) requirement for this application because necessary studies are impossible or highly impracticable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 assess an unexpected serious risk of carcinogenicity with the chronic use of Welireg (belzutifan).

Furthermore, the active postmarket risk identification and analysis system as available 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:

- 4132-1 Conduct a carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on August 11, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2023
Final Protocol Submission:	04/2023
Study Completion:	04/2025
Final Report Submission:	04/2026

- 4132-2 Conduct a carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on August 11, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2023
Final Protocol Submission:	04/2023
Study Completion:	04/2025
Final Report Submission:	04/2026

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of anemia, hypoxia, embryofetal toxicity, and increased incidence and severity of certain adverse events in patients who are treated with Welireg (belzutifan).

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>.

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

- 4132-3 Conduct an analysis from Study MK-6482-004 to further characterize and determine the incidence and severity of anemia, hypoxia, second primary malignancies and other serious adverse events in patients receiving belzutifan. Include incidence rates, time to onset, outcomes, red cell transfusion and the use of erythropoiesis stimulating agents for anemia and steps taken to mitigate these risks in the reports. Provide interim reports annually for 3 years.

The timetable you submitted on August 11 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	04/2022
Interim Report Submission #1:	05/2022
Interim Report Submission #2:	05/2023
Interim Report Submission #3:	05/2024
Trial Completion:	06/2026
Final Report Submission:	12/2026

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.⁴

Submit clinical protocol(s) to your IND 137354 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).

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.

⁴ 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>.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 4132-4 Provide an analysis for the overall response rate and duration of response in all patients and in the subgroups of patients with partial or complete VHL gene deletion, CNS hemangioblastoma, and pNET enrolled in Study MK-6482-004 annually for five years. The study reports should include the number of patients who undergo surgical intervention and/or procedures for renal cell carcinoma (RCC) and/or non-RCC tumors and who develop metastatic RCC.

The timetable you submitted on August 11, 2021, states that you will conduct this study according to the following schedule:

Interim analysis #1:	01/2022
Interim Analysis #2:	01/2023
Interim Analysis #3:	01/2024
Interim Analysis #4:	01/2025
Trial Completion:	06/2026
Final Report Submission:	12/2026

Submit the datasets with the final report.

- 4132-5 Conduct a clinical trial evaluating overall response rate, and duration of response, to further characterize the efficacy and clinical benefit of belzutifan in patients with VHL disease-associated non-RCC tumors, including an adequate number of patients and representation of tumor types, with a minimum of 30 patients in the following subgroups: (1) Pheochromocytoma/paraganglioma and (2) pNET. Characterize response rate and duration of response for at least 24 months from the onset of response.

The timetable you submitted on August 11, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2022
Final Protocol Submission:	05/2022
Trial Completion:	02/2026
Final Report Submission:	08/2026

Submit the datasets with the final report.

- 4123-6 Submit the final objective response rate and duration of response to further characterize efficacy in the subgroup of patients with VHL disease from the phase II clinical trial of belzutifan for treatment of advanced and metastatic pheochromocytoma/paraganglioma or pancreatic neuroendocrine tumor (MK-6482-015, NCT04924075).

The timetable you submitted on August 11, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2022
Trial Completion:	02/2026
Final Report Submission:	08/2026

Submit the datasets with the final report.

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 137354 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**."

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.*⁵

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.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷

REPORTING REQUIREMENTS

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

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, call the Regulatory Project Manager for this application.

If you have any questions, contact Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Deputy Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Carton and Container Labeling

⁵ For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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/

JULIA A BEAVER
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