CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761363Orig1s000

Trade Name:	**Winrevair for injection, for subcutaneous use**
Generic or Proper Name:	**(sotatercept-csrk)**
Sponsor:	**Merck Sharp & Dohme LLC (Merck)**
Approval Date:	**March 26, 2024**
Indication:	**WINREVAIR is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events.**

CENTER FOR DRUG EVALUATION AND RESEARCH

761363Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Integrated Review(s)	**X**
Product Quality Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761363Orig1s000

APPROVAL LETTER

BLA 761363

BLA APPROVAL

Merck Sharp & Dohme, LLC
Attention: Tonja Hampton, MD
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
RY34B-332
Rahway, NJ 07065-0900

Dear Dr. Hampton:

Please refer to your biologics license application (BLA) dated and received July 26, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Winrevair (sotatercept-csrk) for injection, for subcutaneous use.

LICENSING

We have approved your BLA for Winrevair (sotatercept-csrk) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Winrevair under your existing Department of Health and Human Services U.S. License No. 0002. Winrevair is indicated for the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture sotatercept-csrk drug substance at (b) (4) The final formulated drug product will be manufactured and filled at Patheon Italia S.P.A, Monza, Italy. The solvent (sterile Water for Injection pre-filled syringes) will be manufactured and filled at (b) (4) The final formulated drug product and solvent will be labeled and packaged at Merck Sharp and Dohme, LLC, Wilson, NC. You may label your product with the proprietary name, Winrevair, and market it in 45 mg and 60 mg single-dose vials.

DATING PERIOD

The dating period for Winrevair shall be 27 months from the date of manufacture when stored at 2 °C to 8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug

substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C. The dating period for your solvent shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

The expiration date for the packaged product, Winevair, plus solvent, shall be dependent on the shortest expiration date of any component.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not required to submit samples of future lots of Winevair and each kit component to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Winrevair, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use). 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 (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

[1] See 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 at 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 **and** carton and container labeling provided via email submitted on March 20, 2024, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761363**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for sotatercept-csrk was not referred to an FDA advisory committee because no unexpected significant safety or efficacy issues were identified, and no controversial or challenging issues arose 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(s) 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 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 embryo-fetal toxicity associated with the use of sotatercept-csrk.

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

4590-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Winerevair (sotatercept-csrk) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you provided via email on March 15, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2024
Final Protocol Submission:	04/2025
Interim study report[3]:	04/2026
Interim study report:	04/2028
Interim study report:	04/2030
Interim study report:	04/2032
Interim study report:	04/2034
Final Report Submission:	10/2035

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 136150 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. 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 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

[3] Interim or "other" milestones may include interim report submission or subject accrual milestones.
[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.

undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 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 601.70 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 601.70. 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4590-2 Implement a drug product release specification for deliverable volume according to United States Pharmacopoeia <697>.

The timetable you submitted on March 11, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2024

4590-3 Perform supplemental validations for the iCIEF and SEC methods to encompass the full specification range.

The timetable you submitted on March 11, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2025

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]

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

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

REQUESTED PHARMACOVIGILANCE

We request that for the initial 5 years following U.S. approval, you submit all serious cases of bleeding (e.g., fatal and life-threatening bleeding) reported with Winrevair (sotatercept) as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)). Specifically, submit all cases of serious bleeding from your global safety database and/or the published medical literature as 15-day "Alert reports" (as described under 21 CFR 600.80(c)(1)) whether foreign or domestic. Conduct structured follow up of these cases to capture risk factors, clinical course (including monitoring performed), lab results, and management for the bleeding event. If available, provide reporter information to facilitate the collection of follow-up information.

We request that for the initial 5 years following U.S. approval you provide a separate narrative summary and analyses of all cases of serious bleeding in your periodic safety report (e.g., the Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show interval and cumulative data relative to the date of approval of Winrevair (sotatercept-csrk), as well as relative to prior periodic safety reports. The analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

POST APPROVAL FEEDBACK MEETING

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, please call Brian Cooney, Regulatory Project Manager, at (301) 796-0886.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

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/

LISA B YANOFF
03/26/2024 04:08:22 PM