CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000

Trade Name:	PREVYMIS™ tablets, 240 mg and 480 mg and PREVYMIS™ injection for intravenous use, 240 mg/12 mL and 480 mg/24 mL in single-dose vials.
Generic or Proper Name:	letermovir
Sponsor:	Merck Sharp & Dohme Corporation
Approval Date:	November 8, 2017
Indication:	For prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMVseropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

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209939Orig1s000
209940Orig1s000

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APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

NDA APPROVAL

Merck Sharp & Dohme Corporation
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Applications (NDAs) dated and received March 8, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PREVYMIS™ (letermovir) tablets, 240 mg and 480 mg and PREVYMIS™ (letermovir) injection for intravenous use, 240 mg/12 mL and 480 mg/24 mL in single-dose vials.

These new drug applications provide for the use of PREVYMIS™ (letermovir) tablets and injection for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

We have completed our review of these applications, as amended. The applications are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). 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, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on August 22, 2017 and November 7, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDAs 209939 and 209940." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug products when it is available to the following address:

Victoria Tyson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6392
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

ADVISORY COMMITTEE

Your applications for letermovir were not referred to an FDA advisory committee because outside expertise was not necessary; 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, 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 these drug products for this indication have an orphan drug designation, you are exempt from this requirement.

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 assess a signal of a serious risk of virologic failure due to resistance to letermovir.

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 this serious risk.

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

3295-1 Conduct phenotypic analysis of letermovir against human CMV (HCMV) mutants carrying the following pUL56 and pUL89 substitutions using bacterial artificial chromosome technology:

- pUL56: M3V, E237G, C325W, E485G, E485G + SNS445-447 deletion, S255L, Y575C, and R816W.
- pUL89: I531T

Include previously identified substitutions with a range of susceptibilities from low fold change (e.g. pUL56 L257I) to high fold change (e.g. pUL56 C325Y) as references.

The timetable you submitted on November 3, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2018
Study Completion:	10/2019
Final Report Submission:	02/2020

Submit clinical protocol(s) to your IND 104706 with a cross-reference letter to these NDAs. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDAs. 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.

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:

3295-2 Conduct a randomized, double-blind, placebo-controlled trial in cytomegalovirus (CMV) seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT) to evaluate the occurrence of late clinically significant CMV infection when letermovir prophylaxis is extended from 100 to 200 days.

The timetable you submitted on November 3, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2018
Study/Trial Completion:	12/2023
Final Report Submission:	06/2024

3295-3 Submit the final study report and datasets from the proposed clinical trial, P002, entitled, "A Phase 3, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients."

The timetable you submitted on November 3, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2018
Study/Trial Completion:	12/2022
Final Report Submission:	06/2023

3295-4 Conduct an in vitro study to determine if letermovir is an inducer of cytochrome P450 enzymes CYP2C8, CYP2C9, or CYP2C19.

The timetable you submitted on November 3, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2018
Study/Trial Completion:	05/2018
Final Report Submission:	08/2018

Submit clinical protocols to your IND 104706 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to these NDAs. 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 these NDAs. 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. 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 package insert and patient PI 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

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 these products. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 these applications.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
11/08/2017