DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208261

NDA APPROVAL

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated and received May 28, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepatier (elbasvir/grazoprevir) tablet; 50 mg/100 mg.

This new drug application provides for the use of Zepatier (elbasvir/grazoprevir) tablet with or without ribavirin for treatment of chronic hepatitis C virus (HCV) genotypes 1 or 4 infection in adults**.**

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 text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208261**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

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

Nina Mani
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6317
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 application for Zepatier (elbasvir/grazoprevir) was not referred to an FDA advisory committee because this drug is not the first in its class and its safety profile is similar to that of other drugs approved for this indication.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages birth to less than three years because the necessary studies are impossible or highly impracticable. This is because in this age group there is a high rate of spontaneous viral clearance and disease progression is slow for children who develop chronic infection.

We are deferring submission of your pediatric studies for ages three years to less than 18 years 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)(C) of the FDCA. These required studies are listed below.

3008-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection.

Final Protocol Submission: 03/2016
Study Completion: 12/2019
Final Report Submission: 01/2021

3008-2 Collect and analyze long-term safety data from pediatric subjects 3 to 17 years of age enrolled in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation, and characterization of elbasvir and grazoprevir resistance associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission: 03/2016
Study Completion: 12/2022
Final Report Submission: 07/2023

Submit the protocols to your IND 110261, 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 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 serious risk of virologic failure due to treatment-emergent substitutions and cross-resistance.

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.

3008-3 Conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Include cross-resistance analyses with approved NS5A inhibitors.

The timetable you submitted on January 7, 2016 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 03/2016
Study Completion: 12/2016
Final Report Submission: 01/2017

3008-4 Conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Include cross-resistance analyses with approved NS3/4A inhibitors.

The timetable you submitted on January 7, 2016 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 03/2016
Study Completion: 12/2016
Final Report Submission: 01/2017

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 virologic failure and treatment-emergent drug resistant viral populations that may limit re-treatment options in a subset of genotype 1a infected subjects with one or more specific baseline NS5A polymorphism(s).

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

3008-5 Conduct a trial in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if treatment with elbasvir/grazoprevir and ribavirin for at least 16 weeks reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial should have adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

The timetable you submitted on January 12, 2016 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2016
Trial Completion:	07/2018
Final Report Submission:	12/2018

Submit the protocols to your IND 110261, with a cross-reference letter to this NDA. Submit 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)."**

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:

3008-6 Evaluate the effect of SLCO1B1 genotype on grazoprevir pharmacokinetics (PK) and response to elbasvir/grazoprevir treatment in patients with chronic hepatitis C virus infection. To evaluate this effect, either conduct a prospective clinical trial with pharmacokinetic and pharmacodynamic endpoints or a retrospective analysis of previously conducted clinical trials with pharmacokinetic data for which stored biospecimens are available. The trial should be enriched or have sufficient numbers of subjects who are homozygous for reduced function alleles (i.e., N130D and V174A), respectively, to adequately assess whether there are differences in PK and treatment responses.

The timetable you submitted on January 7, 2016 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 05/2016
Final Report Submission: 06/2017

3008-7 Submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 068 (C-EDGE TE).

The timetable you submitted on January 7, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 02/2016

3008-8 Submit the final report and datasets, including the SVR24 data, for Phase 2 Trial 048 (C-SALVAGE).

The timetable you submitted on January 7, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 02/2016

3008-9 Submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 061 (C-EDGE CO-INFECTION).

The timetable you submitted on January 7, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 02/2016

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. 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, Medication Guide, and patient PI (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 (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 this product. 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 this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Nina Mani, Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
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
01/28/2016