

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206843Orig1s000

Trade Name: DAKLINZA tablets 30 and 60 mg

Generic Name: daclatasvir

Sponsor: Bristol-Myers Squibb Company

Approval Date: July 24, 2015

Indication: For the use of DAKLINZA (daclatasvir) in combination with sofosbuvir for the treatment of chronic hepatitis C virus, genotype 3 infection.

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 206843

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Marianne Frost
Director, Global Regulatory, Safety & Biometrics - US
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your New Drug Application (NDA), received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DAKLINZA (daclatasvir) tablets 30 and 60 mg.

We acknowledge receipt of your amendments dated:

February 28, 2014	July 14, 2014	February 13, 2015
March 31, 2014	July 23, 2014	March 2, 2015
April 4, 2014	July 29, 2014	March 6, 2015
April 10, 2014	August 6, 2014	March 20, 2015
April 28, 2014	August 11, 2014	March 27, 2015
April 29, 2014	August 14, 2014	April 9, 2015
May 2, 2014	August 25, 2014 (X2)	April 24, 2015
May 20, 2014	August 26, 2014	April 30, 2015
June 10, 2014	August 29, 2014	May 8, 2015
June 20, 2014	September 11, 2014	May 22, 2015
June 25, 2014	October 9, 2014	June 9, 2015
June 26, 2014	October 23, 2014	June 19, 2015
June 27, 2014	November 19, 2014	June 24, 2015
June 30, 2014	December 8, 2014	July 10, 2015
July 3, 2014	December 15, 2014	July 16, 2015
July 9, 2014	December 22, 2014	July 21, 2015 (X2)
July 10, 2014	January 9, 2015	July 22, 2015

The February 13, 2015, submission constituted a complete response to our November 25, 2014, action letter.

This new drug application provides for the use of DAKLINZA (daclatasvir) in combination with sofosbuvir for the treatment of chronic hepatitis C virus, genotype 3 infection.

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, 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, 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 *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 206843.**” Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for DAKLINZA (daclatasvir) was 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.

We are waiving the pediatric study requirement for ages birth to less than 3 years because necessary studies are impossible or highly impracticable. This is because spontaneous resolution of chronic hepatitis C (CHC) infection is higher in children than in adults.

We are deferring submission of your pediatric study for ages 3 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2930-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of daclatasvir in combination with other direct acting antivirals in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

Final Protocol Submission: 10/31/2019

Study Completion: 07/31/2023

Final Report Submission: 12/31/2023

Submit the protocol to your IND 79,599, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study 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 known serious risk of

virologic failure and persistence of treatment-emergent drug resistant viral populations that may limit re-treatment options, or to assess a known serious risk of severe, life-threatening bradycardia associated with use of amiodarone co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including daclatasvir.

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:

- 2930-2 Conduct an observational study to characterize the long-term (≥ 1 year) persistence of treatment-emergent daclatasvir resistance-associated substitutions in hepatitis C virus genotype 3 infected subjects who failed treatment with daclatasvir-containing treatment regimens.

The timetable you submitted on July 16, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: completed
Study Completion: 09/2017
Final Report Submission: 09/2018

- 2930-3 Evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between amiodarone and HCV direct acting antivirals, including daclatasvir, using a multielectrode array electrophysiology study in human stem-cell derived cardiomyocytes.

The timetable you submitted on July 21, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: completed
Trial Completion: 12/2015
Final Report Submission: 02/2016

- 2930-4 Evaluate the effect of individual HCV direct acting antivirals including daclatasvir on the plasma protein binding of amiodarone using the TRANSIL[®] high sensitivity binding assay to help elucidate the potential mechanism of an interaction between amiodarone and HCV direct acting antivirals.

The timetable you submitted on July 21, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: completed
Trial Completion: 12/2015
Final Report Submission: 02/2016

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 persistence of treatment-emergent drug resistant viral populations in hepatitis C virus genotype 3 (HCV GT3) patients with cirrhosis that may limit re-treatment options.

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

- 2930-5 Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with daclatasvir plus sofosbuvir to determine if a longer duration of treatment or the addition of ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations.

The timetable you submitted on July 16, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2015
Trial Completion:	05/2017
Final Report Submission:	11/2017

Submit the protocol(s) to your IND 79,599, with a cross-reference letter to this NDA. Submit 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.

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.

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.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD
Deputy 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/

JOHN J FARLEY
07/24/2015