CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206843

COMPLETE RESPONSE

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

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

We acknowledge receipt of your amendments dated:

February 28, 2014,	June 25, 2014	August 6, 2014
March 31, 2014	June 26, 2014	August 11, 2014
April 4, 2014	June 27, 2014	August 14, 2014
April 10, 2014	June 30, 2014	August 25, 2014 (X2)
April 28, 2014	July 3, 2014	August 26, 2014
April 29, 2014	July 9, 2014	August 29, 2014
May 2, 2014	July 10, 2014	September 11, 2014
May 20, 2014	July 14, 2014	October 9, 2014
June 10, 2014	July 23, 2014	October 23, 2014
June 20, 2014	July 29, 2014	November 19, 2014

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You submitted two NDAs; NDA 206843 for daclatasvir and NDA 206844 for asunaprevir. The proposed indication for both NDAs was for the treatment of chronic hepatitis C virus infection. The pivotal data to support safety and efficacy for each drug came from three Phase 3 trials which evaluated the combination of daclatasvir and asunaprevir or the combination of daclatasvir and asunaprevir in combination with pegylated interferon alpha and ribavirin (P/R). Thus, both NDA's shared the same three pivotal phase 3 trials. On October 6, 2014, you withdrew the asunaprevir application. As a result, the daclatasvir NDA does not contain adequate evidence to establish the safety and efficacy of daclatasvir without asunaprevir for the treatment of chronic hepatitis C virus infection.

Before the application can be approved, it will be necessary for you to provide clinical data to support the safety and efficacy of daclatasvir in combination with other antiviral agents for the treatment of chronic hepatitis C virus infection.

PRESCRIBING INFORMATION

2. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

   If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

PROPRIETARY NAME

3. Please refer to correspondence dated, May 02, 2014 which addresses the proposed proprietary name, Daklinza. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials (from the on-treatment period) for the proposed indication using a format that DAVP agrees upon prior to submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- Please note that safety data from the original NDA includes the safety data provided in the safety update report and only safety data subsequent to the safety update report cut dates would be considered new safety data. Additionally, we are requesting that only on-treatment safety data be provided in detail as highlighted in this section and only important new safety findings or trends during the post-treatment period be highlighted in a separate post-treatment safety findings section.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events, any grade 3 or 4 liver event not otherwise covered by discontinuation, SAE or death and any hypersensitivity events with or without liver involvement.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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 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

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
11/25/2014