CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206545Orig1s000

Trade Name: Zydelig Tablets

Generic Name: idelalisib

Sponsor: Gilead Sciences, Inc.

Approval Date: July 23, 2014

Indications: Provides for the use of Zydelig (idelalisib) tablets for relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

CENTER FOR DRUG EVALUATION AND RESEARCH

206545Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics 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:

206545Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206545

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Lauren Cutler, MS, RAC
Manager, Regulatory Affairs
199 East Blaine Street
Seattle, WA 98102

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated December 6, 2013, received December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zydelig (idelalisib) Tablets.

We acknowledge receipt of your amendments dated December 11, 13, and 16, 2013; January 9, 23, 28, and 31; February 4, 14, and 21; March 10, 21, 24, and 31; April 7 (2), 15, 17, and 23; May 5, 8, 9, 15, 21, and 27; June 2 (2), 3, 9, 17, and 20; and July 2, 3, 15, 17, 18, 21 and 22, 2014.

This new drug application provides for the use of Zydelig (idelalisib) tablets for relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

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 text.

Please refer to the action letter issued today for Zydelig (idelalisib), NDA 205858, for the relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) indications.

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 Medication

Guide). 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.

IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed 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 206545**." 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 Zydelig (idelalisib) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 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 assess signals of the serious risks of hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious and fatal risks of hepatotoxicity, severe diarrhea or colitis, and intestinal perforation, which should be characterized in longer term safety assessments of Zydelig (idelalisib), when used alone or in combination with other therapies. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2180-8 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with an anti-CD20 drug regimen. Submit the complete final report and data from trial GS-US-312-0119, a Phase 3, randomized, study of idelalisib in combination with ofatumumab in patients with previously treated CLL.

The timetable you submitted on July 17, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion:	04/2015
Interim Follow-up Report Submission:	12/2017
Final Report Submission:	12/2019

PMR 2180-9 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in a combination therapy regimen. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-312-0117, a Phase 3, 2 arm, extension study of idelalisib in patients with previously treated CLL.

The timetable you submitted on July 17, 2014, states that you will conduct this trial according to the following schedule:

Interim Follow-up Report Submission:	12/2017
Trial Completion:	06/2019
Final Report Submission:	12/2019

We have now administratively closed this NDA. Submit all protocols and protocol amendments to your IND 101254**,** with a cross-reference letter to NDA **205858**. Submit all interim and final reports to NDA **205858**. 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Zydelig (idelalisib) to ensure the benefits of the drug outweigh the risks of fatal and serious events with Zydelig (idelalisib) treatment including hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation.

We have determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on July 22, 2014 and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Zydelig (idelalisib) Tablets into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of prescribers awareness and understanding of the risks associated with Zydelig and the management of these events:

    - Fatal and/or serious hepatotoxicity

    - Fatal and/or serious and severe diarrhea or colitis

- Fatal and serious pneumonitis
- Fatal and serious intestinal perforation

2. A description of the implementation of the communication plan, including:

    - Number of healthcare providers and professional societies targeted by the REMS
    - Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via mail because the emailed letter was undeliverable. Also include numbers of returned or undeliverable letters. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients.
    - The sources of the distribution lists
    - Date journal pieces appeared in each journal or publication, including volume, issue number, and name
    - Date and name of the scientific meetings attended and materials displayed
    - Date the REMS website went live, and number of unique site visits to the Zydelig REMS website during the assessment period.
    - Number of REMS fact sheets distributed by Gilead representatives during follow-up details/visits with healthcare providers during the 12 months after approval of the REMS.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 205858 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 205858 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 205858
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 205858
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

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).

We have now administratively closed this NDA. Therefore, all 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original **NDA 205858** for this drug product, not to this NDA. In the future, do not make submissions to this NDA **except** for the final printed labeling requested above.

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 Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Office Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Container Labeling
REMS

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

/s/

RICHARD PAZDUR
07/23/2014