

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205858Orig1s000

Trade Name: Zydelig

Generic Name: Idelalisib

Sponsor: Gilead Sciences, Inc.

Approval Date: July 23, 2014

Indications: Zydelig is a kinase inhibitor indicated for the treatment of patients with:

- 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.
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies.
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

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APPROVAL LETTER



NDA 205858

ACCELERATED 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 September 11, 2013, received September 11, 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 September 19; October 15, 16, and 28; November 1, 7, 8, and 9; December 2, 5, 6, 11, 16, 20, and 22, 2013; January 3, 6, 8, 9, 17, 22, 27, 28, and 31; February 4, 13, 18, and 21; March 10, 12, 18, 21, 24, and 29; April 7 (2), 15, 16, 17, and 22; May 5, 8, 9, 15, 21, 28, and 30; June 2, 3, 9, 11, 17, 20; and July 2, 3, 15, 17, 18, 21 and 22, 2014.

This NDA provides for the use of Zydelig (idelalisib) for relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies and relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

Please refer to the action letter issued today for Zydelig (idelalisib), NDA 206545, for the relapsed chronic lymphocytic leukemia indication.

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 titled “SPL Standard for Content of Labeling Technical Qs and As” 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 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 titled “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 205858.**” 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.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated July 17, 2014. These requirements, along with required completion dates, are listed below.

PMR 2180-1 Design and conduct a prospective trial and provide the full final report and data sets to evaluate dose reductions in patients who achieve a response or have stable disease in order to optimize the safety and efficacy of chronic administration of Zydelig in patients with follicular or small lymphocytic lymphoma. Include adequate PK sampling to provide dose-response data (for efficacy and safety).

Final Protocol Submission: 12/2014
Interim Report Submission: 12/2017
Trial Completion: 06/2019
Final Report Submission: 12/2019

PMR 2180-2 Submit the complete final report and data showing clinical efficacy and safety from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group trial of idelalisib in combination with rituximab in subjects with previously treated indolent non-Hodgkin lymphomas.

Trial Completion: 12/2017
Final Report Submission: 01/2018

PMR 2180-3 Submit the complete final report and data showing clinical efficacy and safety from trial GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group trial of idelalisib in combination with bendamustine plus rituximab in subjects with previously treated indolent non-Hodgkin lymphomas.

Trial Completion: 02/2019
Final Report Submission: 08/2019

Successful completion of either PMR 2180-2 or PMR 2180-3 may be adequate, after review, to convert the accelerated approval to regular approval for relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies and for relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

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 the known risk of pneumonitis.

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:

PMR 2180-4 Conduct a study to characterize the incidence, diagnosis, and effective treatment of Zydelig-related pneumonitis based on data and pooled analyses from randomized trials in iNHL and CLL (0115, 0119, 0124, and 0125).

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

Analysis Plan Submission:	10/2014
Interim Report Submission:	06/2015
Interim Report Submission:	06/2016
Interim Report Submission:	06/2017
Study Completion:	05/2020
Final Report Submission:	11/2020

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 2180-5 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial 101-99 Phase 1/2 extension study of safety and durability of idelalisib in hematologic malignancies.

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

PMR 2180-6 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in patients with previously treated indolent non-Hodgkin lymphomas.

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

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

PMR 2180-7 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with other agents such as bendamustine (B) and rituximab (R). Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in patients with previously treated indolent non-Hodgkin lymphomas.

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:	02/2019
Final Report Submission:	12/2019

Submit the protocols and protocol amendments to your IND 101254, with a cross-reference letter to this NDA. Submit all interim and final reports to your 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

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with the 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 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