DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205858/S-009

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

Gilead Sciences, Inc.
Attention: Marissa Braff, PhD
Associate Director, Regulatory Affairs
199 East Blaine Street
Seattle, WA 98102

Dear Dr. Braff:

Please refer to your Supplemental New Drug Application (sNDA) dated September 20, 2017, received September 20, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zydelig® (idelalisib) tablets, 100 mg and 150 mg.

This Prior Approval supplemental new drug application provides for revisions to:

- Update the United States Prescribing Information (USPI) per the Pregnancy and Lactation Labeling Rule;
- Update the USPI, under the Dosage and Administration section, to include information regarding lymphocytosis;
- Update the USPI with data from the study reports of Postmarketing Requirements (PMR) 2180-2, 2180-3, 2180-4, 2180-6, and 2180-7, including safety information related to hepatoxicity, severe diarrhea or colitis, pneumonitis, infections, and neutropenia;
- Add the following Limitation of Use to the USPI and Medication Guide: Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of follicular lymphoma; and
- Update the approved Zydelig risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental 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 Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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 none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submissions dated June 30 and October 11, 2017, containing the third interim report for the following postmarketing requirement listed in the July 23, 2014 approval letter.

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).

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

We have reviewed your submission and conclude that the October 11, 2017 submission can be accepted as the final report for the above PMR and the above requirement was fulfilled.

RELEASE FROM POSTMARKETING REQUIREMENT

We have received your submission dated January 26, 2017 reporting on the following post-marketing requirements listed in our July 23, 2014 approval letter:

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

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.

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.

Interim Follow-up Report Submission:	12/2017
Trial Completion:	02/2019
Final Report Submission:	12/2019

We have reviewed your submission and have determined that you are released from the above postmarketing requirements for the following reason: Trials GS-US-313-0124 and GS-US-313-0125 were terminated early due to increased serious adverse events and infection-related deaths in patients on the Zydelig arms compared to the control arm. FDA determined that the combination of Zydelig with rituximab for lymphoma and the combination of Zydelig with rituximab and bendamustine for lymphoma resulted in an unacceptable incidence of early toxic deaths. FDA conducted additional subgroup analyses using patient-related and disease-related factors, and found no subpopulation that did not have a substantial risk of toxicity or that tolerated the currently recommended dose well. Therefore, sufficient information regarding clinical benefit or long-term safety cannot be obtained from these PMRs.

The above postmarketing requirements will be replaced by the new postmarketing requirement as described below:

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.510, withdraw this approval. We remind you of your post-marketing requirement specified in your submission dated January 24, 2018. This requirement, along with required completion dates, is listed below.

PMR 2180-10 Conduct a trial establishing a safe and effective dosing regimen of idelalisib in patients with relapsed or refractory follicular lymphoma (FL) who have no other therapeutic options and require treatment. Include a dosing regimen arm with a

21-day of a 28-day treatment cycle. The primary efficacy endpoint should be overall response rate (ORR). There should be sufficient follow-up to provide a credible assessment of duration of response (DOR). A dosing regimen of idelalisib will be considered to be effective in relapsed/refractory FL if the ORR is greater than 50% with a DOR of at least 6 months. The primary safety endpoint should be incidence of grade 4 and 5 treatment emergent adverse events (TEAE). A dosing regimen of idelalisib will be considered safe in this patient population if the rate of grade 4 and 5 TEAE is less than 30%.

Draft Protocol Submission:	05/2018
Final Protocol Submission:	12/2018
Trial Completion:	04/2024
Final Report Submission:	10/2024

Submit clinical protocols to your IND 101254 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) you should include a status summary of each requirement 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.

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)**."

Under section 505(p)(2), failure to conduct a postmarketing study or trial required under subparts H and E (21 CFR 314.510 and 601.41) may result in enforcement action.

We remind you that there are postmarketing requirements listed in the July 23, 2014 approval letter that are still open.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Zydelig was originally approved on July 23, 2014, and the most recent REMS modification was approved on January 4, 2017. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of safety related updates to the REMS materials regarding the risk of fatal and/or serious hepatoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and/or serious pneumonitis, and fatal and/or serious infections associated with Zydelig, and the addition of the following Limitation of Use: Zydelig is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of follicular lymphoma.

Your proposed modified REMS, submitted on September 20, 2017, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on January 4, 2017.

There are no changes to the REMS assessment plan described in our January 4, 2017 letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that 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. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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

NDA 205858 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 205858/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205858/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205858/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 205858/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 205858

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any

new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Quyen Tran, Regulatory Project Manager, at (301) 796-2771.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of 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/

ALBERT B DEISSEROTH
01/26/2018