DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205858/S-005

SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION

Gilead Sciences, Inc.
Attention: Pierre Kiami, MPH, RAC
Associate Manager, Regulatory Affairs
199 East Blaine Street
Seattle, WA 98102

Dear Mr. Kiami:

Please refer to your Supplemental New Drug Application (sNDA) dated September 22, 2016, received September 22, 2016, 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.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated June 20, 2016.

This Prior Approval supplemental new drug application provides for modification to the approved risk evaluation and mitigation strategy (REMS) for Zydelig® (idelalisib) to align with safety labeling changes that were approved on September 21, 2016, under S-004.

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.

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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Zydelig® (idelalisib) was originally approved on July 23, 2014. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of changes to the REMS materials based on the safety labeling changes approved on September 21, 2016, including the addition of a new risk (fatal and/or serious infections) to the REMS goal statement, and a change to the timetable for submission of REMS assessments.

Your proposed modified REMS, submitted on September 22, 2016, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to change the next assessment due date from 3 years from the date of initial approval, to 4 years from the date of initial approval of the REMS (July 23, 2014).

In order to align with the modified REMS, the REMS assessment plan is being revised. The revised REMS assessment plan must include, but is not limited to, the following:

- An evaluation of prescribers awareness and understanding of the risks associated with Zydelig and the management of these risks including:
    - Fatal and/or serious hepatotoxicity
    - Fatal and/or serious and severe diarrhea or colitis
    - Fatal and/or serious pneumonitis
    - Fatal and/or serious infections
    - Fatal and serious intestinal perforation
- 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. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients. Include the number of letters sent via mail because the emailed letter was undeliverable or the email unknown. For letters sent by mail include numbers of returned or undeliverable letters.
    - The sources of the distribution lists

- Date journal pieces appeared in each journal or publication, including volume and issue number

- Name and date of scientific meetings 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

- Number of REMS wallet cards distributed by Gilead representatives during follow-up details/visits with healthcare providers.

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 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 of 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 the 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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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

NEW SUPPLEMENT FOR NDA 205858
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205858
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205858

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 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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 Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Barry W. Miller
Acting Deputy Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

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

/s/

BARRY W MILLER
01/04/2017