

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206545Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206545

SUPPL #

HFD # 161

Trade Name Zydelig

Generic Name Idelalisib

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known July 23, 2014 Also see approval for NDA 205858 dated July 23, 2014.

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

Also see approval letter for NDA 205858 dated July 23, 2014.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:



Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

MARA B MILLER  
07/23/2014

EDVARDAS KAMINSKAS  
07/23/2014

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 206545 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): 1

Division Name: DHP PDUFA Goal Date: 8/6/2014 Stamp Date: 12/6/2013

Proprietary Name: Zydelig

Established/Generic Name: Idelalisib

Dosage Form: Tablets

Applicant/Sponsor: Gilead Sciences, Inc

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** 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.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PerRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cdernmhs@fda.hhs.gov](mailto:cdernmhs@fda.hhs.gov)) OR AT 301-796-0700.

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

---

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible*	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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

/s/  
-----

MARA B MILLER  
07/22/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206545 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zydelig Established/Proper Name: Idelalisib Dosage Form: Tablets		Applicant: Gilead Sciences, Inc Agent for Applicant (if applicable):
RPM: Mara Miller		Division: Division of Hematology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)                      Date of check:                 </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 6, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		N/A
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other – ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) July 23, 2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included July 21, 2014
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included December 16, 2013
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included July 21, 2014
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included February 21, 2014
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included July 15, 2014
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	March 16, 2014 March 11, 2014
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: Memo July 17, 2014 DMEPA: April 7, 2014 DMPP/PLT: June 26, 2014 OPDP: June 25, 2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	February 4, 2014
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u></li> </ul> </li> </ul>	<p>Pediatric Page- July 22, 2014</p>
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<p>July 21 (3), 18, 16 (2), 11, and 2, 2014; June 27, 13 and 3, 2014; May 22 (2), 20, and 14, 2014; April 17 (2), 14, and 1, 2014; March 28, 19, 10, and 5 2014; February 11 and 10, 2014; January 27, 9, 7, and 2 (2), 2014; December 27 and 17, 2013; November 27 (2), 22, 19, 13 and 7, 2013; October 31, 28, 21, 18, 9 (2), 7, and 4, 2013; and September 13, 2013</p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<p>July 1, 2013</p>
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<p>February 25, 2014</p>
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<p>June 5, 2014</p>
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<p>July 22, 2014</p>
<p>Division Director Summary Review (<i>indicate date for each review</i>)</p>	<p>July 15, 2014</p>
<p>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</p>	<p>July 7, 2014</p>
<p>PMR/PMC Development Templates (<i>indicate total number</i>)</p>	<p>See NDA 205858</p>
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review Co-signed June 3, 2014 review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	<p>Review: June 3, 2014 Filing: January 14, 2014</p>
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	<p>See page 17 of Clinical Review dated June 3, 2014</p>

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	July 22, 2014; May 30, 2014; May 28, 2014  July 22, 2014  July 21, 2014; June 27, 2014; May 21, 2014
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	June 4, 2014; May 5, 2014; April 16, 2014; April 16, 2014
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Co-signed May 21, 2014 Review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Co-signed May 21, 2014 Review
Statistical Review(s) ( <i>indicate date for each review</i> )	Review: May 21, 2014 Filing: January 29, 2014
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Co-signed May 15, 2014 Review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	Review: May 15, 2014 QT/IRT: January 3, 2014 Filing: January 17, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	Memo: May 01, 2014
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	Filing: February 3, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review Co-signed May 12, 2014 Review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Review: May 12, 2014 Biopharm Review: May 13, 2014 Filing: January 31, 2014
❖ <b>Microbiology Reviews</b>	
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	Review: January 2, 2014 Filing: January 31, 2014
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ <b>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i></b>	
	<input checked="" type="checkbox"/> None
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See May 12, 2014 Product Quality Review, Page 123-124
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ <b>Facilities Review/Inspection</b>	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: May 19, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ <b>NDAs: Methods Validation <i>(check box only, do not include documents)</i></b>	
	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	N/A – Orphan Designation
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/  
-----

MARA B MILLER  
07/23/2014

**From:** Miller, Mara Bauman  
**To:** ["Lauren Cutler"](#)  
**Subject:** RE: Zydelig NDA 205858 and 206545 FDA Final PI  
**Date:** Monday, July 21, 2014 2:35:00 PM

---

Hi Lauren,

The team has reviewed Gilead's suggested edit and agrees that the text can be changed to 1 Gi/L.

Thank you,  
Mara

---

**From:** Lauren Cutler [mailto:[Lauren.Cutler@gilead.com](mailto:Lauren.Cutler@gilead.com)]  
**Sent:** Monday, July 21, 2014 12:24 PM  
**To:** Miller, Mara Bauman  
**Subject:** RE: Zydelig NDA 205858 and 206545 FDA Final PI

Hi Mara-

Gilead noticed a small error:

In section 5.7 for Neutropenia it says: "Monitor blood counts at least every two weeks for the first 3 months of therapy, and at least weekly in patients while neutrophil counts are less than 1000 Gi/L [see *Dosage and Administration (2.2)*]."

We believe this should be 1 Gi/L based Table 1 on 2.2?

Neutropenia	ANC 1.0 to <1.5 Gi/L	ANC 0.5 to <1.0 Gi/L	ANC <0.5 Gi/L
	Maintain Zydelig dose.	Maintain Zydelig dose. Monitor ANC at least weekly.	Interrupt Zydelig. Monitor ANC at least weekly until ANC $\geq$ 0.5 Gi/L, then may resume Zydelig at 100 mg BID.

Since this wasn't one of the changes sent back by FDA we aren't sure how to go about making the change. Can we make the change and still submit as final?

Thanks!

Lauren Cutler  
Manager, Regulatory Affairs  
Gilead Sciences, Inc.  
Ph: 206-832-2049  
Fax: 206-832-2011  
[lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)

---

**From:** Miller, Mara Bauman [mailto:[Mara.Miller@fda.hhs.gov](mailto:Mara.Miller@fda.hhs.gov)]  
**Sent:** Monday, July 21, 2014 6:55 AM  
**To:** Lauren Cutler  
**Subject:** Zydelig NDA 205858 and 206545 FDA Final PI

Hello Lauren,

The FDA accepts the changes proposed by Gilead in the PI received via email on Friday July 18, 2014. Please note the few formatting comments in the highlights and minor corrections to references in section 5.0. Please submit the final agreed upon PI and Medication Guide to the NDA.

Thank you,  
Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
07/21/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cuttler@lead.com](mailto:lauren.cuttler@lead.com)  
**Subject:** Zydelig REMS documents and comments  
**Date:** Monday, July 21, 2014 1:45:00 PM  
**Attachments:** [zydelig-rems-tracked FDA 7.21.14.doc](#)  
[zydelig-rems-supporting-document-tracked 7.22.14.docx](#)  
[zydelig HCP REMS Letter electronic tracked FDA 7.21.14.docx](#)  
[Zydelig HCP REMS Letter print-tr cked FDA 7.21.14.docx](#)  
[Zydelig Patient Safety Information Card tracked FDA 7.21.14.doc](#)  
[Zydelig Prof Soc REMS Letter electronic tracked FDA 7.21.14.docx](#)  
[Zydelig Prof Soc REMS Letter print tracked FDA 7.21.14.docx](#)  
[Zydelig REMS Fact Sheet tracked FDA 7.21.14.docx](#)  
[Zydelig REMS Journal Piece tracked FDA 7.21.14.docx](#)  
[Zydelig REMS Website landing page tracked FDA 7.21.14.docx](#)  
[Zydelig REMS Website landing page layout FDA 7.21.14.pdf](#)  
[Zydelig Patient Safety Information Card layout FDA 7.15.14.pdf](#)  
**Importance:** High

Hello Lauren,  
Attached are the FDA's comments on the Zydelig REMS. See general comments and specific comments below as well as the attachments.  
Thanks,  
Mara

**1 General comments:**

DRISK finds the outline and layout of the revised REMS, REMS Supporting Document, and the print versions of the REMS letters acceptable. The layouts of the electronic versions of the REMS Letters, the Zydelig Patient Safety Information Card, the REMS Journal Information Piece, and the Website Landing Page must be revised. Ensure that all REMS materials align with language from the final approved label and **return via email to Mara Miller by July 22, 2014 at 12:00 PM EST**. Address all comments noted in the redlined documents of your submission and bubble comments inserted into pdf layout versions of the selected materials attached. Accept all changes and submit Word tracked changes versions and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents. A mock up version that includes colorings and logos in Adobe pdf format of the REMS communication materials with the updated language should also be submitted. All REMS materials that contain the Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength as this is also included in the label. Note that the REMS materials are not appropriate for use in a promotional manner.

**2 REMS document:**

See the attached REMS document with the necessary changes with comments and edits in track changes. Of note, language has been included in the Patient Safety Information Card section to delineate how healthcare providers will obtain the patient safety information cards to give to patients who are prescribed Zydelig. The timetable for submission of assessments has been changed to 18 months, 3 years, and 7 years.

**3 REMS Supporting Document:**

See the attached REMS Supporting Document with the necessary changes with edits in track changes to align with labeling and the REMS document.

**4 REMS Letters (email and print):**

See the attached REMS letters with the necessary changes in track changes. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

**5 REMS Letters (email versions):**

See the attached email template for the letters Gilead will send electronically to HCPs and Professional Societies. An example with appropriate language for the subject line and body of the email has been attached for your review. The electronic version of the REMS letters should be email and handheld-device friendly. The goal is to have this information in the body of an email, versus an attachment. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

**6 REMS Fact sheet:**

The REMS Fact sheet should be printed on thicker card stock paper with updated formatting, including logo changes for the Zydelig REMS program as stated above. See the attached REMS Fact Sheet with the necessary changes with edits in track changes.

**7. Zydelig REMS Website**

Place [this text](#) in the purple banner header copy: "Zydelig (idelalisib) REMS (Risk Evaluation and Mitigation Strategy)" and ~~delete~~ this text: "Zydelig (idelalisib) REMS". As a result, there will not be a subhead on the website landing page. Ensure that only the final approved Important Safety Information, Medication Guide, and Prescribing Information are available on the Zydelig REMS website. Add the following text to the journal information piece: "You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088."

The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

Make additional changes to the website landing page as noted in the attached MS Word document and the comments on the adobe pdf Layout document.

**8 REMS Journal Information Piece:**

Delete the title (b) (4) at the top of the journal piece. The title "FDA REQUIRED Safety Information for Zydelig (idelalisib)" should be placed in the purple banner box instead. The Zydelig logo with the 150 mg strength must be updated to also include the 100 mg strength.

Add the following text to the bottom of the journal information piece: "You are encouraged to report negative side effects of Zydelig to Gilead at 1-800-445-3235 and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088."

See the attached REMS Journal Information Piece with additional edits in track changes.

**9 Zydelig Patient Safety Information Card:**

Switch the information for the patient with that for the physician, but keep the text on both purple right columns as is. In other words, the patient's name, prescriber's name, etc., should be to the right of and on the same side of the card as the information for the treating physician. This card should be printed on thicker card stock paper so that it may be durable and easy to carry for patients. The Zydelig logo with the 150mg strength must be updated to also include the 100mg strength.

See the attached Patient Safety Information Card for additional comments and edits in track changes.

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

/s/  
-----

MARA B MILLER  
07/21/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** Zydelig NDA 205858 and 206545 FDA Final PI  
**Date:** Monday, July 21, 2014 9:54:00 AM  
**Attachments:** [ZydeligPI\\_FDAFINAL\\_21JUL14.doc](#)

---

Hello Lauren,

The FDA accepts the changes proposed by Gilead in the PI received via email on Friday July 18, 2014. Please note the few formatting comments in the highlights and minor corrections to references in section 5.0. Please submit the final agreed upon PI and Medication Guide to the NDA.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

23 Pages Of Draft Labeling Have Been Withheld As b4 (CCI/TS) Immediately Following  
This Page

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

/s/  
-----

MARA B MILLER  
07/21/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Bcc:** [Davis, Kathleen](#)  
**Subject:** Zydelig PI - FDA Comments  
**Date:** Friday, July 18, 2014 11:09:00 AM  
**Attachments:** [ZydeligPI\\_FDAComments\\_18JUL14.doc](#)  
**Importance:** High

---

Dear Lauren,

Attached are the FDA's comments on the Zydelig PI for NDAs 205858 and 206545. Please review and accept the changes or comment if there is not an agreement.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Please review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website and use the Selected Requirements for Prescribing Information (SRPI) checklist to ensure that the PI conforms with the format items in regulations and guidances.

Provide a response **by 4:30 PM EST today 7/18/14**. With your response, submit the SAS code used to generate Figure 1.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

23 Pages Of Draft Labeling Have Been Withheld As b4 (CCI/TS) Immediately Following This Page

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

/s/  
-----

MARA B MILLER  
07/18/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** Zydelig PI- FDA Comments  
**Date:** Wednesday, July 16, 2014 1:02:00 PM  
**Attachments:** [ZydeligPI\\_FDAComments\\_16JUL14.doc](#)  
[Zydelig\\_MedGuide\\_16JUL14.docx](#)  
**Importance:** High

---

Hello Lauren,

Attached is the current version of the PI with FDA Comments. Please accept those changes agreed upon and comment on those not agreed to. Provide a response by Thursday 7/17/2014 at 2:00 PM EST.

In addition, the medication guide attached has been agreed to and is considered final. When you submit the PI officially to the NDA upon final agreement, also submit this version of the Medication Guide.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
07/17/2014

24 Pages Of Draft Labeling Has Been Withheld As b4 (CCI/TS) Immediately Following This Page

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 205858 and NDA 206545 Zydelig- PMRs  
**Date:** Wednesday, July 16, 2014 9:48:00 AM  
**Attachments:** [Zydelig\\_PMRS\\_16JUL14.docx](#)  
**Importance:** High

---

Hello Lauren,

Attached are the FDA's final comments on the PMRs for these two NDAs. Please accept agreements and comment on disagreements. If final agreement has been reached, please submit the final PMR text officially to the NDAs.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

4 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately Following  
This Page

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

/s/  
-----

MARA B MILLER  
07/17/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** Zydelig- FDA Comments on PI and Medication Guide  
**Date:** Friday, July 11, 2014 1:47:00 PM  
**Attachments:** [MedicationGuide FDAComments 11JUL2014.docx](#)  
[ZydeligPI FDAComments 11JUL14.doc](#)

---

Hello Lauren,

Attached are the current FDA comments on the PI and Medication Guide. Please accept changes Gilead agrees with and comment on those FDA does not agree with (keep track changes for disagreements). Please respond by Wednesday July 16, 2014 at 3:00 PM EST.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

30 Pages Of Draft Labeling Has Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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

/s/  
-----

MARA B MILLER  
07/17/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** Zydelig PMRs- FDA Comments  
**Date:** Wednesday, July 02, 2014 3:05:00 PM  
**Attachments:** [NDA 205858\\_FDAComments\\_PMR\\_02JUL14.docx](#)  
[NDA 206545\\_FDAComments\\_PMRs\\_02JUL14.docx](#)  
**Importance:** High

---

Hello Lauren,

Attached are the FDA comments to the proposed draft PMRs as revised by Gilead and received June 9, 2014. Accept changes Gilead agrees to and comment on those Gilead does not agree to.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Final PMR designation numbers will be assigned later.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

4 Pages Of Draft Labeling Has Been Withheld In Full As b4 (CCI/TS) Immediately Following  
This Page

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

/s/  
-----

MARA B MILLER  
07/02/2014

**From:** [McMullen, Rachel](#)  
**To:** [Lauren Cutler \(Lauren.Cutler@gilead.com\)](mailto:Lauren.Cutler@gilead.com)  
**Cc:** [Miller, Mara Bauman](#)  
**Subject:** NDA 205858 and NDA 206545\_FDA comments on REMS, response needed by July 2nd  
**Date:** Friday, June 27, 2014 2:46:26 PM  
**Attachments:** [REMS 26 6 2014 FDA edits.doc](#)  
[REMS Supporting Document FDA edits 6 26 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig HCP REMS letter electronic version HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig HCP REMS letter print version HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig Prof Soc REMS letter electronic version HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig Prof Soc REMS letter print version HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig REMS envelope HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig REMS Fact Sheet HCA Review 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig REMS Journal Piece HCA Review B 6 24 14.docx](#)  
[Gilead Sciences NDA 205858 and 206545 Zydelig REMS Website landing page HCA Review 6 24 14.docx](#)  
[Zydelig Patient Safety Information Card C .doc](#)

**Importance:** High

---

Dear Lauren,

Please refer to your pending NDA 205858 and NDA 206545 for Zydelig (idelalisib).

The Division of Risk Management (DRISK) has reviewed your REMS documents included in your submission from May 21, 2014. Please see the comments below and specific FDA revisions noted in the attached documents.

Please review and submit all documents based on the updated changes as outlined below. Please send your response via email to [Mara.Miller@fda.hhs.gov](mailto:Mara.Miller@fda.hhs.gov) and via electronic gateway submission by **Wednesday, July 2<sup>nd</sup>, 2014.**

1. **General comments:**

- a. FDA finds the outline of the REMS document, REMS supporting document, and the REMS communication tools which includes the REMS letter to healthcare providers (email and print versions), REMS letter to professional societies (email and print versions), REMS Fact sheet, REMS journal information piece, and REMS website generally acceptable. However, significant revisions to the language for these documents must align with the most recent label submission on June 17<sup>th</sup>, 2014. Please address all comments noted in the redlined documents of your submission, accept all changes, and submit both a Word tracked changes versions and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents. A mock up version in Adobe pdf format of the REMS communication materials with the updated language should also be submitted.
- b. The REMS Journal Piece refers to [www.Zydelig.com](http://www.Zydelig.com) and the DHCP letters and DPS letters refer to [www.gilead.com](http://www.gilead.com). REMS materials should only include a web address which represents a direct link to the REMS materials (such as [www.ZydeligREMS.com](http://www.ZydeligREMS.com)). The web address should not represent the commercial or promotional website for the product. Establish

a separate domain for the Zydelig REMS website immediately upon approval.

- c. In addition, DRISK and DHP have concluded that inclusion of a patient safety information wallet card with updated language from the label submitted on June 17, 2014 should be included as part of the REMS communication tools. (See below).
- d. Ensure that all materials reflect the final approved label. Incorporate all edits based on the specific track changes in each document as outlined below. The REMS materials are not appropriate for use in a promotional manner.

2. **REMS document:**

See the attached REMS document with the necessary changes with comments and edits in track changes.

3. **REMS Supporting Document:**

See the attached REMS Supporting Document with the necessary changes with edits in track changes to align with labeling. Of note, language is included to assist with formulating your assessment plan for the REMS document.

4. **REMS Letter to Healthcare Providers (email and print):**

See the attached REMS letters with the necessary changes with edits in track changes.

5. **REMS letter to Professional Societies (email and print):**

See the attached REMS letters with the necessary changes with edits in track changes.

6. **REMS Envelope:**

See the attached REMS envelope with the necessary changes with edits in track changes.

7. **REMS Fact sheet:**

See the attached REMS Fact Sheet with the necessary changes with edits in track changes.

8. **Zydelig REMS Website**

Make changes to the website landing page as noted in the attached MS Word document.

9. **REMS Journal Information Piece:**

See the attached REMS Journal Information Piece with the necessary changes with edits in track changes.

10. **Zydelig Patient Safety Information Card:**

Create a patient safety information card based on text in the attached MS Word document, formatted very similarly to that for Soliris®. This card should highlight the risks and include information on the management of these risks. It should include red and yellow colors, a white cross, and a danger symbol similar to Solaris to alert emergency personnel as to its importance. This card should be given to all patients by Zydelig prescribers and should be carried by patients on Zydelig at all times. Patients should be clearly instructed to show this card to any healthcare professional that treats them. The patient safety information card should also be available on the Zydelig REMS website as a pdf for downloading. This card may be foldable and printed on the front and back if needed - so that it may comfortably fit in a standard wallet. A pdf of the Soliris® Patient Safety Information Card is attached for your reference.

-

-

Please confirm receipt of this email correspondence.

Kind Regards,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

---

**From:** Redd, Naomi  
**Sent:** Friday, June 27, 2014 2:12 PM  
**To:** McMullen, Rachel  
**Cc:** Miller, Mara Bauman; Wright, Kevin; Auth, Doris  
**Subject:** DRISK comments to the sponsor for idelalisib NDA 205858 and NDA 206545

Hello Rachel,  
Please forward the comments I have drafted below and the attached documents regarding the REMS submission to Gilead by close of business today.  
Thank you, and have a great weekend.  
-Naomi

---

Below are comments regarding the REMS submission on May 21, 2014. Please review and submit all documents based on the updated changes as outlined below

via email to [Mara.Miller@fda.hhs.gov](mailto:Mara.Miller@fda.hhs.gov) and via electronic gateway submission by **Wednesday, July 2<sup>nd</sup>**.

1. **General comments:**

- a. FDA finds the outline of the REMS document, REMS supporting document, and the REMS communication tools which includes the REMS letter to healthcare providers (email and print versions), REMS letter to professional societies (email and print versions), REMS Fact sheet, REMS journal information piece, and REMS website generally acceptable. However, significant revisions to the language for these documents must align with the most recent label submission on June 17<sup>th</sup>, 2014. Please address all comments noted in the redlined documents of your submission, accept all changes, and submit both a Word tracked changes versions and a Word clean version of each document, as well as a cover letter explaining all changes proposed in the documents. A mock up version in Adobe pdf format of the REMS communication materials with the updated language should also be submitted.
- b. The REMS Journal Piece refers to [www.Zydelig.com](http://www.Zydelig.com) and the DHCP letters and DPS letters refer to [www.gilead.com](http://www.gilead.com). REMS materials should only include a web address which represents a direct link to the REMS materials (such as [www.ZydeligREMS.com](http://www.ZydeligREMS.com)). The web address should not represent the commercial or promotional website for the product. Establish a separate domain for the Zydelig REMS website immediately upon approval.
- c. In addition, DRISK and DHP have concluded that inclusion of a patient safety information wallet card with updated language from the label submitted on June 17, 2014 should be included as part of the REMS communication tools. (See below).
- d. Ensure that all materials reflect the final approved label. Incorporate all edits based on the specific track changes in each document as outlined below. The REMS materials are not appropriate for use in a promotional manner.

2. **REMS document:**

See the attached REMS document with the necessary changes with comments and edits in track changes.

3. **REMS Supporting Document:**

See the attached REMS Supporting Document with the necessary changes with edits in track changes to align with labeling. Of note, language is included to assist with formulating your assessment plan for the REMS document.

4. **REMS Letter to Healthcare Providers (email and print):**

See the attached REMS letters with the necessary changes with edits in track changes.

5. **REMS letter to Professional Societies (email and print):**

See the attached REMS letters with the necessary changes with edits in track changes.

6. **REMS Envelope:**

See the attached REMS envelope with the necessary changes with edits in track changes.

7. **REMS Fact sheet:**

See the attached REMS Fact Sheet with the necessary changes with edits in track changes.

8. **Zydelig REMS Website**

Make changes to the website landing page as noted in the attached MS Word document.

9. **REMS Journal Information Piece:**

See the attached REMS Journal Information Piece with the necessary changes with edits in track changes.

10. **Zydelig Patient Safety Information Card:**

Create a patient safety information card based on text in the attached MS Word document, formatted very similarly to that for Soliris®. This card should highlight the risks and include information on the management of these risks. It should include red and yellow colors, a white cross, and a danger symbol similar to Solaris to alert emergency personnel as to its importance. This card should be given to all patients by Zydelig prescribers and should be carried by patients on Zydelig at all times. Patients should be clearly instructed to show this card to any healthcare professional that treats them. The patient safety information card should also be available on the Zydelig REMS website as a pdf for downloading. This card may be foldable and printed on the front and back if needed - so that it may comfortably fit in a standard wallet. A pdf of the Soliris® Patient Safety Information Card is attached for your reference.

-  
-

Naomi S. Redd, Pharm.D  
Drug Risk Management Analyst  
Food and Drug Administration  
Center for Drug and Evaluation Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Division of Risk Management

10903 New Hampshire Avenue, Bldg 22, Room 2485  
Silver Spring, MD 20993-0002  
301-796-5791

54 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MARA B MILLER  
06/30/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Cc:** [Jennifer.Stephens \(jennifer.Stephens@gilead.com\)](mailto:Jennifer.Stephens@gilead.com)  
**Subject:** Zydelig NDA 205858 and 206545- FDA Comments on PI  
**Date:** Friday, June 13, 2014 2:12:00 PM  
**Attachments:** [Zydelig\\_PI\\_FDAComments\\_03Jun14.doc](#)  
**Importance:** High

---

Hello Lauren,

Attached are FDA's current edits/comments on the PI. Gilead should accept those changes they agree with and comment on those changes they do not agree with (do not reject FDA revisions, leave in track changes and add comments and edit in track changes).

Please provide a response by June 23, 2014.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MARA B MILLER  
06/13/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545 PMR Discussion  
**Date:** Tuesday, June 03, 2014 1:23:00 PM  
**Attachments:** [NDA206545\\_PMRs.doc](#)

---

Dear Lauren,

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the attached clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category. (However, PREA Milestones require month, day, and year.) For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMR/PMCs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to your application. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.
2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
  - a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
  - b. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to your application officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and cover letter to your application that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

1 Page Of Draft Labeling Has Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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

/s/  
-----

MARA B MILLER  
06/03/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.culler@gilead.com](mailto:lauren.culler@gilead.com)  
**Subject:** Zydelig NDA 205858 and NDA 206545 Information Request  
**Date:** Thursday, May 22, 2014 3:07:00 PM

---

Hello Lauren,

Regarding your submission dated May 21, 2014 containing the revised PI and proposed REMS, we have the following information request. Please provide a response with the REMS materials and revised PI by Tuesday May 27, 2014.

- Your proposed revisions for the boxed warning and warnings and precautions sections of the PI are inadequate. Submit revised versions (highlights and FPI) of the boxed warning and warnings and precautions to include more detailed information regarding the frequency, severity, presenting signs and symptoms, outcomes, and management of the toxicities.
- Submit mock-up versions of all REMS materials (REMS Letters, Factsheet, Journal Information Piece, REMS Website landing page)
- **REMS Letters:** Replace the use of a standard Dear Healthcare Provider (DHCP) letter with concise, risk-focused REMS letters addressed to healthcare providers and relevant Professional Societies. FDA proposes having the REMS letters formatted in two different ways: print and electronic versions. Send mock-up versions of both. The electronic version of the REMS letters should be email and handheld device-friendly. The heading of the print version of the REMS letter should be printed in red, bolded, and minimum size 14 font that states: "FDA Required REMS Safety Information." The outside of the mailed envelopes should state: "FDA Required REMS Safety Information," be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

FDA Required REMS

Safety  
Information

- **REMS Factsheet for Healthcare Providers:** Create a REMS Factsheet for healthcare providers. This REMS Factsheet must be in a user-friendly format, including coloring, and any logos from the Zydelig REMS program. Include bullets, boxes, and bold text to highlight important information; have plenty of white space and a font size of at least 12; be printed on thicker card stock paper; be only one sheet with information on both sides of the paper, and the heading should read: "FDA Required Zydelig REMS Safety Information."
- **Journal Information Piece:** Create a journal information piece that outlines the risk included in the Zydelig REMS. Include coloring and any logos from the Zydelig REMS program; bullets, boxes, and bold text to highlight important information; have plenty of white space and a font size of at least 12. The statement: "This journal information piece is part of the FDA required Zydelig REMS. For complete safety information, see the Prescribing Information available at [www.ZydeligREMS.com](http://www.ZydeligREMS.com)" must be included on the journal information piece.
- **REMS Website:** Ensure the Zydelig REMS website is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the Zydelig REMS website back to the Zydelig promotional website. The Zydelig REMS website should also be accessible directly through a search engine.
- Submit all REMS materials including the REMS document and a REMS Supporting Document in MS Word format.
- Please note: Language in all REMS materials must reflect what is in approved final labeling.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
05/22/2014



NDA 206545

**DISCIPLINE REVIEW LETTER**

Gilead Sciences, Inc.  
Attention: Lauren Cutler, M.S., 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 for Zydelig<sup>®</sup> (idelalisib) Tablets.

Our review of your submission is complete, and we have identified the following deficiencies:

**CLINICAL**

1. Your proposed labeling instructs users to continue treatment until disease progression or unacceptable toxicity, but the NDA included safety data on relatively few subjects treated with Zydelig for more than 6 months. You will need to submit data that support the safety of long-term use of Zydelig for the treatment of CLL with at least 5 years of follow-up.
2. Your safety data includes cases of severe or life-threatening pneumonitis. Your proposed labeling indicates [REDACTED] (b)(4). You will need to conduct a study to characterize the incidence, diagnosis and effective treatment of idelalisib-related pneumonitis.
3. Your proposed labeling includes several dose modifications to avoid or to relieve serious or life-threatening complications of Zydelig. You will need to develop a communication plan to warn healthcare providers about the risks, recommended monitoring and dose modifications to mitigate serious or life-threatening toxicities.
4. In your clinical trials, use of Zydelig was associated with a substantial risk of serious toxicities that were moderated by treatment interruption. Zydelig is an oral agent used continuously in the outpatient setting outside the direct supervision of a healthcare provider. To ensure safe use of Zydelig, you will need to develop a Patient Medication Guide.

5. Your proposed labeling indicates that severe diarrhea due to Zydelig resolved with drug interruption and additional treatment [REDACTED] (b) (4). You will need to provide data showing that [REDACTED] (b) (4) contributed to resolution of diarrhea rather than just interruption of use of Zydelig.

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

R. Angelo de Claro, MD  
Cross Discipline Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology 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/  
-----

ROMEO A DE CLARO  
05/20/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** Information Request- Zydelig  
**Date:** Wednesday, May 14, 2014 10:06:00 AM  
**Importance:** High

---

Hello Lauren,

See information request for NDA 205858 and 206545. Please submit a response by 12:00 PM EST, Thursday, May 15.

IR to NDA 205858

1. Submit a letter of cross-reference to NDA 205858 that allows the Agency to reference information submitted to IND 101254 or NDA 206545.
2. Submit the MedWatch forms (or equivalent) for all cases of bowel perforation that has occurred in Zydelig-treated patients, regardless of attribution. Include a brief summary of the cases of bowel perforation.

IR to NDA 206545

1. Submit a letter of cross-reference to NDA 206545 that allows the Agency to reference information submitted to IND 101254 or NDA 205858.
2. Submit the MedWatch forms (or equivalent) for all cases of bowel perforation that has occurred in Zydelig-treated patients, regardless of attribution. Include a brief summary of the cases of bowel perforation.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
05/14/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545- Information Request  
**Date:** Thursday, May 01, 2014 4:08:00 PM  
**Attachments:** [Type I Error Rate.pdf](#)  
**Importance:** High

---

Hello Lauren,

We have the following information requests with regard to your simulation study investigating the type I error rate for the secondary endpoint OS in Study 312-0116. Please submit a response prior to start of business on Monday May 5, 2014 (9:00 am EST).

1. You have used Figure 3 and 4 in Efficacy information amendment document to claim that type I error rate is controlled.
  - In Figure 3 the average type I error rates are plotted and does not include the variability. When the HR for PFS is 0.28 (upper 95% CL), in fact type I error is not controlled at 2-sided 0.05 level based on Figure 3. Furthermore, the PFS estimate is based on an interim analysis and it is well recognized that the interim analysis results overestimate treatment effect size.( Also, it is anticipated that the type I error rate for the third secondary endpoint, OS, should be much higher using threshold of 0.05 for all secondary endpoints since the analysis did not consider there are two additional secondary endpoints that have hierarchical order ahead of OS)
  - In Figure 4, the simulations are based on post-hoc threshold value and this was not pre-specified.
2. In your simulation study, you assumed that PFS and OS follow a bivariate normal distribution. Please provide justification to the assumption, in particular for OS where the information is limited and majority of the observations are censored very early.
3. The type I error rate can be analytically derived using the approach specified in the attached document. Please derive the type-I error for OS using the formula mentioned in the document.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products

WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
05/01/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Thursday, April 17, 2014 5:20 PM  
**To:** lauren.cutler@gilead.com  
**Cc:** Akinsanya, Lara; Miller, Mara Bauman  
**Subject:** Clinical Information Request - Gilead Sciences, Inc NDA 205858 and 206545/Idelalisib - Due Monday, 4/21

Dear Lauren

Please respond to the below Clinical Information Request by **Monday, April 21, 2014**:

- Explain the terms spleen response LVD and liver response LVD used in the ADRS dataset. How do these terms relate to spleen actual LVD and liver actual LVD?
- Submit a dataset, as a SAS transport file (.xpt), which contains the following information from clinical trial 312-0116: USUBJID, Treatment arm, absolute neutrophil count (ANC), peripheral blood ALC, platelet count, and hemoglobin at each study visit. The dataset should include a flag field to indicate if a value or change from baseline met criteria for response.
- Submit a dataset as a SAS transport file (.xpt) for all patients with disease progression, which indicates which criteria were met for disease progression and the date of progression. The following disease progression criteria should be included in the dataset (with a column for each criteria):
  - a new node >1.5cm
  - a new node > 1cm to  $\geq 1.5$ cm in the longest diameter and > 1 cm in the longest perpendicular diameter
  - new hepatomegaly
  - new splenomegaly
  - new non-index disease
  - worsening increase  $\geq 50\%$  from the nadir in SPD of index lesions
  - increase  $\geq 50\%$  from a single lesion that now meets definition of abnormal
  - increase  $\geq 50\%$  from nadir in longest diameter of any individual node that now has perpendicular diameter > 1.0 cm
  - increase  $\geq 50\%$  from nadir spleen enlargement by palpation
  - Increase  $\geq 50\%$  from nadir spleen enlargement by imaging
  - increase  $\geq 50\%$  from nadir liver enlargement by percussion
  - Increase  $\geq 50\%$  from nadir liver enlargement by imaging
  - Increase in size of non-index disease
  - Transformation to a more aggressive histology
  - Decrease > 50% in platelet count to  $< 100 \times 10^9/L$
  - Decrease in hemoglobin by 2 g/dL to  $< 11$  g/dL
- The protocol states in section 7.5.2, that for a partial response all of the following criteria must be met and must persist for  $\geq 8$  weeks, while the Imaging Charter states in section 13.5.7 that PR will be based on a change in disease status meeting  $\geq 2$  of the following criteria. Conduct an analysis of response rate based on the criteria specified in the protocol. Only patients that met criteria for response and had documented confirmation of response  $\geq 8$  weeks later should be counted as responders.

- For patients that had disease progression based on platelet or hemoglobin criteria, submit a dataset as a SAS transport file (.xpt), which contains the following information from clinical trial 312-0116: USUBJID, Treatment arm, platelet count, hemoglobin, and transfusion at each study visit. The dataset should include a flag field to indicate if a value or change from baseline met criteria for disease progression.
- Provide a CRF for the following subjects: 7065-10301, 7061-10270, 2870-10002, 2870-10606

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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

/s/  
-----

MONSURAT O AKINSANYA  
04/18/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Thursday, April 17, 2014 5:26 PM  
**To:** lauren.cutler@gilead.com  
**Cc:** Akinsanya, Lara; Miller, Mara Bauman  
**Subject:** Statistics Information Request - Gilead Sciences, Inc NDA 205858 and 206545/Idelalisib  
- Due Friday 4/18

Dear Lauren

Please respond to the below Information Request by your COB **Friday, April 18, 2014:**

We have the following information requests with regard to your simulation study investigating the type I error rate for the secondary endpoint OS in Study 312-0116.

1. Submit the program codes (e.g. SAS program codes) that were used to calculate and plot the type I error rate for OS.
2. Clarify how treatment effect expressed in Z scale is obtained. In your example, the estimated treatment effect on the primary endpoint as measured in hazard ratio (HR) is 0.15 (95% CI: 0.08, 0.28). Clarify how you obtain that the treatment effect of 5.96 (95% CI: 4.00, 7.93).

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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

/s/  
-----

MONSURAT O AKINSANYA  
04/18/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 205858 and 206545 Labeling Comments  
**Date:** Friday, March 28, 2014 10:58:00 AM  
**Attachments:** [Zydelig\\_draft-labeling-text\\_FDAedits\\_28MAR14.docx](#)  
**Importance:** High

---

Hello Lauren,

Attached are the FDA's edits and comments on the draft PI for Zydelig. Please accept the changes that Gilead agrees with and comment on the changes that Gilead does not agree with. In addition, update the Medication Guide in accordance with the draft PI.

Provide Gilead's comments by COB Pacific on Friday April 4, 2014.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MARA B MILLER  
03/28/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545 Information Request  
**Date:** Tuesday, March 25, 2014 9:02:00 AM  
**Importance:** High

---

Regarding NDA 206545, we have the following information request. Please provide a response by Friday March 28, 2014.

- Submit all laboratory values using ADLB dataset format, including bilirubin results, for subject 7064-10646 for the following dates: 8/5/13-8/20/2013.
- Submit a narrative for subject 7064-10646 that covers the following time period: 8/5/13-8/20/2013. Describe any clinical signs or symptoms the subject experienced.
- Submit all laboratory values using ADLB dataset format, including bilirubin results, for subject 7141-10417 for the following dates: 6/25/13-8/6/13
- Submit a narrative for subject 7141-10417 that covers the following time period: 6/25/13-8/6/13. Describe any clinical signs or symptoms the subject experienced.
- Submit all laboratory values using ADLB dataset format, including bilirubin results, for subject 5776-10214 for the following dates: 2/2/13-2/9/13.
- Submit all laboratory values using ADLB dataset format, including bilirubin results, for subject 5775-10633 for the following dates: 7/2/13-7/18/13.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
03/25/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206545

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Gilead Sciences, Inc.  
199 East Blaine Street  
Seattle, WA 98102

Attention: Lauren Cutler  
Manager, Regulatory Affairs

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 for Idelalisib Tablets, 100 mg and 150 mg.

We also refer to your January 9, 2014, correspondence, received January 9, 2014, requesting review of your proposed proprietary name, Zydelig. We have completed our review of the proposed proprietary name, Zydelig, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sonny Saini, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0532. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Mara Miller at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, PharmD., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
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/  
-----

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
03/16/2014



NDA 205858 and 206545

**MID-CYCLE COMMUNICATION**

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Idelalisib tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 25, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

R. Angelo de Claro, MD  
Clinical Team Lead  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** February 25, 2014 3:00 -4:00 PM EST

**Application Number:** NDA 205858 and NDA 206545

**Product Name:** Idelalisib

**Indication:** iNHL and CLL

**Applicant Name:** Gilead Sciences

**Meeting Chair:** R. Angelo de Claro, MD

**Meeting Recorder:** Mara Miller, MA

**FDA ATTENDEES**

Office of Hematology and Oncology Products

Jonathan Jarow, MD, Associate Director (Acting)

Division of Hematology Products

Ann Farrell, MD, Division Director

Robert Kane, MD, Deputy Director for Safety

R. Angelo de Claro, MD, Clinical Team Lead

Barry Miller, MS, CRNP, Clinical Reviewer

Nicole Gormley, MD, Clinical Reviewer

Qin Ryan, MD, PhD, Safety Reviewer

Mara Miller, MA, Regulatory Project Manager

Diane Leaman, BS, Safety Project Manager

Lara Akinsnaya, MS, Regulatory Project Manager

Tinya Sensie, MHA, Regulatory Project Manager

Division of Hematology Oncology Toxicology

Haleh Saber, PhD, Supervisory Pharmacologist

Ramadevi Gudi, PhD, Reviewer

Office of Clinical Pharmacology

Julie Bullock, PharmD, Clinical Pharmacology Team Lead

Stacy Short, PharmD, Clinical Pharmacology Reviewer

Nitin Mehrotra, PhD, Pharmacometrics Team Lead

Dhanajay Marathe, PhD, Pharmacometrics Reviewer

Office of New Drug Quality Assessment

Janice Brown, MS, Team Lead

Debasis Ghosh, PhD, Reviewer

Office of Biostatistics

Yuan Li Shen, PhD, Team Lead (Acting)

Kyung Y Lee, PhD, Reviewer

Sirisha Mushti, PhD, Reviewer

Office of Surveillance and Epidemiology

Steven Bird, MD, Team Lead

Naomi Redd, PharmD, Reviewer

Tracy Salaam, PharmD, Reviewer

Office of Prescription Drug Promotion

Richard Lyght, PharmD, Reviewer

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (4) Independent Assessor

(b) (4) Independent Assessor

**APPLICANT ATTENDEES**

Roger Dansey, MD, VP, Oncology Clinical Research

Lynday Dreiling, MD, Senior Director, Oncology Clinical Research

Terry Newcomb, PhD, Senior Director, Oncology Clinical Research

Xiaomign Li, PhD, Director, Biostatistics

Daniel Li, PhD, Senior Manager, Biostatistics

Jing Hu, PhD, Senior Manager, Biostatistics

Srinivasan Ramanathan, PhD, Director, Clinical Pharmacology

Philippe Carriere, MD, Director, Drug Safety and Public Health

Christopher Aguilar, MD, Associate Director, Drug Safety and Public Health

Jason Chamberlain, PhD, MBA, Senior Research Scientist I, Drug Safety Evaluation

Michael Kernan, PhD, Senior Director, Analytical Development

Regan Shea, PhD, VP, Pharmaceutical Development and Manufacturing

Bill Donaldson, Senior Director, Regulatory Affairs

Jennifer Stephens, Director, Regulatory Affairs

Linda McBride, RPh, Associate Director, Regulatory Affairs CMC

Dawne Hom, Senior Manager, Regulatory Affairs CMC

Lauren Cutler, MBS, Manager, Regulatory Affairs

**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

### Clinical

- Regarding the indolent lymphoma indication, the enrolled population consists primarily of patients with follicular lymphoma (58%) and small lymphocytic lymphoma (22%). The small numbers of other histologic lymphoma subtypes will likely not support labeling for these indications.
- Regarding the CLL indication, as mentioned in prior communication, CIRS does not identify a population of patients who would not be eligible for standard chemotherapy. Additional information (requested 02/25/14) will be needed to delineate the appropriate population for labelling.
- There are concerns that Rituximab alone may not be an appropriate comparator given the current standards of care.

### Statistical Issues for CLL clinical trial

- There are 44 patients censored for PFS at day 1. Based on the first interim analysis data cutoff date (8/30/2013), these patients were newly enrolled prior to the cutoff date and had not reached the first tumor assessment time (i.e. every 8 weeks) except two patients. As a result, it is noted that these patients may not contribute any information for the first interim analysis for PFS.
- Some supporting data may not be fully captured. Incomplete data were identified in data such as baseline characteristics (e.g. screening Binet and Rai staging, etc), concomitant medication, etc.
- Whether or not the OS result is sufficient for including into the labeling will be subject to further discussion.

## 3.0 INFORMATION REQUESTS

- Product quality will request additional drug substance information. We anticipate the CMC information request will be sent in early March.

## 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The prescribing instructions state that treatment with idelalisib should continue until disease progression or unacceptable toxicity, but the duration of exposure in the pivotal trial is relatively short for the majority of the subjects. Data to support safety of long-term use is deficient. The clinical team discussed that further discussions will occur to address this deficiency during the labeling and PMR/PMC negotiation period.

Additional studies might be needed to further evaluate the effect of idelalisib on the pharmacokinetics of drugs predominantly metabolized by CYP29 and CYP2C19 based on in vitro studies that suggest that idelalisib inhibits CYP2C19 and GS-563117 inhibits CYP2C9 and CYP2C19.

An additional study might be needed to further evaluate the effect of acid-reducing agents on the pharmacokinetics of idelalisib, as idelalisib demonstrates pH dependent solubility and the solubility appears to be lower than the estimated concentration of idelalisib in the stomach following the proposed dose of 150 mg.

## 5.0 RISK MANAGEMENT UPDATE

The review teams have determined that a Medication Guide is needed in order to ensure safe and effective use of idelalisib. The clinical team informed the Sponsor that the reason for this recommendation would be more apparent

once the labeling is sent back to the Sponsor. The clinical team requested that further discussion regarding the Medication Guide be conducted during the period of labeling negotiations.

The review teams have made a preliminary determination that a REMS is not needed for this application.

## **6.0 ADVISORY COMMITTEE MEETING**

An AC meeting is not planned at this time.

## **7.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

- a. Projected Date for Late Cycle Meeting: Tentatively Mid May
- b. Projected Date for Labeling/PMR/PMC Discussion: Tentatively Mid April
- c. Action Date: To Be Determined based on completion of reviews and negotiations of labeling and PMRs and PMCs.

The Sponsor requested clarification regarding the timing of action for both applications. Dr. de Claro, the cross-disciplinary team lead for both NDAs (205858 and 206545) stated that the current plan would be to take concurrent action for both applications.

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

/s/  
-----

ROMEO A DE CLARO  
03/06/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545- Information Request  
**Date:** Tuesday, February 25, 2014 8:49:00 AM

---

Hello Lauren,

Regarding NDA 206545, we have the following information request. Please provide a response by COB (Pacific) March 10, 2014.

- Submit a dataset as a SAS transport file (.xpt), with one row per subject that contains the following information from clinical trial 312-0116: USUBJID, Treatment arm, Flag indicating which criteria allowed subject to enter study (myelotoxic effects of prior chemotherapy, CrCl  $\leq$ 60 mL/min, or CIRS >6), CrCl at screening, CIRS score at screening, absolute neutrophil count (ANC) at screening, ANC grade at screening, platelet count at screening, and platelet grade at screening.
- Submit a dataset as a SAS transport file (.xpt), with information detailing subsequent therapies received by patients that progressed. This information can be submitted in the format used for the concomitant medications dataset.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
02/25/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545 and NDA 205858- Information Request  
**Date:** Tuesday, February 11, 2014 3:26:00 PM

---

Hello Lauren,

Regarding both NDA 205858 and NDA 206545, please submit a draft Medication Guide according to 21 CFR Part 208. Submit the medication guide to both NDAs by February 24, 2014.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
02/11/2014



NDA 205858 and 206545

**INFORMATION REQUEST**

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Idelalisib 100 mg and 150 mg Tablets.

We are reviewing your submission and have the following comments and information requests. Please provide a response by March 21, 2014.

1. The provided dissolution data do not support the selection of your proposed acceptance. Implement the following dissolution acceptance criterion for your proposed product and provide the updated specifications table for your product with the revised recommended acceptance criterion.

<b>Recommended Acceptance criterion</b>
Q= (b) (4) % in 20 min

2. If available, provide data showing the ability of the proposed dissolution method and acceptance criterion to reject batches that are not bioequivalent.
3. Provide data (tabular and graphical form) on the effect of the following material attributes and process parameters on the dissolution profiles of your proposed product:
  - o Drug substance particle size (d10 and d50)
  - o Tablet hardness in the range tested ( (b) (4) kP)
  - o Percent weight gain in the range tested ( (b) (4) %)

- o [REDACTED] <sup>(b) (4)</sup> in the ranges tested
4. Provide rationale for the high variability in dissolution profiles observed in the batches manufactured at the [REDACTED] <sup>(b) (4)</sup> (refer to Figures 1 and 2, submission dated 12/16/13).

If you have any questions, call me at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

Mara Miller, M.A.  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology 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/  
-----

MARA B MILLER  
02/10/2014



NDA 206545

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Gilead Sciences, Inc.  
Attention: Lauren Cutler, M.S., 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, for Zydelig (Idelalisib).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is August 6, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 9, 2014. In addition, the planned date for our internal mid-cycle review meeting is March 6, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **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 the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology 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/  
-----

ANN T FARRELL  
02/03/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545 Information Request  
**Date:** Wednesday, January 29, 2014 7:30:00 AM

---

Hello Lauren,

Regarding NDA 206545, we have the following information request. Please provide a response by COB (Pacific) on February 4, 2014.

- Submit a dataset as a SAS transport file (.xpt), with one row per subject that contains the following information from clinical trial 312-0116: USUBJID, Treatment arm, Any Dose Modification (Y/N), Dose reduction (Y/N), dose interruption (Y/N), number of days with any dose modification, number of days with a dose reduction, number of days with a dose interruption.
- For Study 312-0116, submit a table that delineates CRFs for each of the following categories: deaths, serious adverse events, and discontinuations due to adverse events
- In the ADEX dataset for Study 312-0116, it is noted that there are several subjects with overlapping administration time frames, resulting in double counting of exposure days ( eg. subjects: 8453-10101, 7060-10403). Please correct this throughout the dataset such that for each subject, each administration day is represented in only one row (one administration analysis time period).

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
01/29/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** RE: NDA 206545, Information Request  
**Date:** Friday, January 17, 2014 4:09:00 PM

---

Hello Lauren,

We have two additional information requests for which we would like a response in the same timeframe as the below response:

1. Reanalyze the LNR endpoints based on the ITT population.
2. Please provide the first interim and second interim data unblinding dates.

Thank you,

Mara

---

**From:** Miller, Mara Bauman  
**Sent:** Thursday, January 16, 2014 10:52 AM  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545, Information Request  
**Importance:** High

Dear Lauren,

Regarding NDA 206545 for Idelalisib, we have the following information request. Please provide a response by January 23, 2014.

1. *In dataset ADEFF for second interim, FDA obtained n=109 and 108 for Idela and Rituxan arm, respectively, using variable TRTP, for (b) (4) based on ITT population. In particular, the subjects subjid=5833-10273, 5833-10275 from Placebo arm and subjid=7291-10689 from the IDELA arm are missing in the ADEFF dataset when subsetted for (b) (4) ). Please clarify the discrepancy of these n with the n used in the labeling.*
2. *Please re-derive the overall survival analysis variables in ADTTE dataset without including the extension study 0117 and submit the SAS programs as well as the revised dataset including the new derived variables.*

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309

10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
01/17/2014

**From:** Miller, Mara Bauman  
**To:** [lauren.cutler@gilead.com](mailto:lauren.cutler@gilead.com)  
**Subject:** NDA 206545, Information Request  
**Date:** Thursday, January 16, 2014 10:51:00 AM  
**Importance:** High

---

Dear Lauren,

Regarding NDA 206545 for Idelalisib, we have the following information request. Please provide a response by January 23, 2014.

- 1. In dataset ADEFF for second interim, FDA obtained n=109 and 108 for Idela and Rituxan arm, respectively, using variable TRTP, for (b) (4) based on ITT population. In particular, the subjects subjid=5833-10273, 5833-10275 from Placebo arm and subjid=7291-10689 from the IDELA arm are missing in the ADEFF dataset when subsetted for (b) (4). Please clarify the discrepancy of these n with the n used in the labeling.*
- 2. Please re-derive the overall survival analysis variables in ADTTE dataset without including the extension study 0117 and submit the SAS programs as well as the revised dataset including the new derived variables.*

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
(301) 796-0683 (phone)

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

/s/  
-----

MARA B MILLER  
01/16/2014



NDA 206545

**NDA ACKNOWLEDGMENT**

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

Dear Ms. Cutler:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Idelalisib 100 mg and 150 mg Tablets

Date of Application: December 6, 2013

Date of Receipt: December 6, 2013

Our Reference Number: NDA 206545

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 4, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

Mara Miller, M.A.  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology 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/  
-----

MARA B MILLER  
12/19/2013



IND 101254

**MEETING MINUTES**

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

Dear Ms. Cutler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Idelalisib.

We also refer to the meeting between representatives of your firm and the FDA on October 7, 2013. The purpose of the meeting was to discuss the early termination of GS-US-312-0116 for efficacy based on the initial interim analysis in progression free survival (PFS).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4969.

Sincerely,

*{See appended electronic signature page}*

Amy Baird  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** Other

**Meeting Date and Time:** October 7, 2013  
**Meeting Location:** WO22, Conference Room 2201

**Application Number:** IND 101254  
**Product Name:** Idelalisib  
**Indication:** Treatment of relapsed and refractory chronic lymphocytic leukemia (CLL)  
**Sponsor/Applicant Name:** Gilead Sciences, Inc.

**Meeting Chair:** R. Angelo De Claro  
**Meeting Recorder:** Amy Baird

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

Richard Pazdur, MD, Director

**Division of Hematology Products**

Ann T. Farrell, MD, Director

Edvardas Kaminskas, MD, Deputy Director

R. Angelo De Claro, MD, Clinical Team Leader

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader

Nicole Gormley, MD, Medical Officer

Barry Miller, MS, CRNP, Senior Clinical Analyst

Mara Bauman Miller, Regulatory Project Manager

Amy Baird, Regulatory Project Manager

**Division of Biometrics 5**

Rajeshwari Sridhara, PhD, Division Director

Thomas Gwise, PhD, Supervisor

Lei Nie, PhD, Team Leader

Chia-Wen Ko, PhD, Reviewer

**Division of Clinical Pharmacology 5**

Julie Bullock, PharmD, Team Leader

## **SPONSOR ATTENDEES**

Roy Baynes, Senior Vice President, Oncology and Inflammation Therapeutics  
David Pizzuti, Vice President, Regulatory Affairs  
Michael Wulfsohn, Vice President, Biometrics

## **1.0 BACKGROUND**

Idelalisib is a selective phosphatidylinositol 3-kinase (PI3K) inhibitor which is expressed in cells of hematopoietic origin. PI3K modulates cellular functions of motility, proliferation, survival and recruitment of additional intracellular signaling enzymes through the B-cell receptor (BCR) which is a pathologic mechanism in B-cell malignancies causing leukemia and lymphoma cell survival and proliferation. Disruption of BCR signaling can be lethal to malignant B cells. Idelalisib is an orally bioavailable drug with proposed dosing of 150mg bid and is being developed for CLL and iNHL.

As of July 2013, clinical trial experience included >600 patients with hematologic malignancies: 352 with single agent idelalisib and 290 with combination treatments. There are four ongoing phase 3 trials with idelalisib in patients with previously treated CLL. Three trials are a randomized double blind add-on design using rituximab, bendamustine + rituximab, or ofatumumab. The fourth is an extension study of single agent idelalisib.

From the sponsor's integrated safety analysis, 98% of patients on single agent idelalisib 150 mg bid (n=206) experienced an AE. The most frequent were diarrhea 37%, fever 29%, fatigue 28%, cough 28%, nausea 27%, neutropenia 23%. AEs occurring in 10-20% of patients included increased ALT and AST, rash, thrombocytopenia, anemia, URI, pneumonia, dyspnea, chills, night sweats, vomiting, decreased appetite, abdominal pain, constipation, back pain, headache, and peripheral edema. Grade  $\geq 3$  AEs occurred in 71% of patients; the most common were neutropenia 15%, increased ALT 11%, and pneumonia 11%.

In this same population, 70 patients (20%) discontinued treatment due to AEs; the most frequent being increased ALT, increased AST, pneumonia, and diarrhea. In the combination therapy population a total of 89 patients (31%) discontinued treatment due to AEs: the most frequent being diarrhea, rash, and colitis.

Of the patients receiving single agent idelalisib, 174 (50%) experienced an SAE, most frequently pneumonia, diarrhea, febrile neutropenia, and pyrexia. In the combination therapy population, 181 patients (62%) experienced an SAE, most frequently pneumonia, pyrexia, febrile neutropenia, diarrhea, and colitis. Twentyfour patients (6%) experienced an AE leading to death. Five patients had pneumonia, three had multi-organ failure, two had *Pneumocystis* pneumonia, and two had septic shock.

## 2. DISCUSSION

***Question 1: Does the Division agree that the data from the interim analysis of Study GS-US-312-0116 demonstrates a sufficiently favorable benefit: risk profile to warrant early termination of the trial while preserving the ability of the data to support an NDA?***

**FDA Response to Question 1:**

It appears that IDELA + rituximab demonstrates a significant improvement in PFS over placebo + rituximab in the interim analysis recognizing that the treatment effect as stated in the interim analysis could be overestimated.

We agree that the trial GS-US-312-0116 can be stopped at your own risk. Please note the results will be viewed as from an interim analysis. Please also note that the follow-up is short with about 40% of the censored events in the IDELA + rituximab arm are censored before 2 months. Risk-benefit will be a review issue.

At the time of submission of the NDA, please provide necessary documents, including DMC meeting minutes and your communication with all personnel to whom the treatments assignments were made available before the interim analysis, as well as who had access to data and analysis results to alleviate potential concerns of bias in relation to some of the major protocol amendments listed below.

- June 26, 2013 submission of Amendment 3 in which you added two interim analyses for the first time.
- Aug 6, 2013 submission of SAP.
- September 2013 submission of Amendment 4 in which you switched the order of the secondary endpoints and made changes for the emergency unblinding.

Please note that the Agency's assessment of benefit-risk is based on review of the primary data. Whether the interim results from your trial support the filing of an application will be determined at the time of submission.

Please discuss your plans for further efficacy and safety follow-up should you decide for early stopping of Study GS-US-312-0116.

***Question 2: Should Gilead decide to stop Study GS-US-312-0116 early, does the Division agree that the data cutoff for the final analysis should occur as soon as possible?***

**FDA Response to Question 2:**

At the meeting, please discuss your timeline for submission of the data and study report for Study GS-US-312-0116. We recommend submission of the data and study report for Study GS-US-312-0116 prior to December 2013 as this will strengthen your current application.

**FDA has no objection to the stopping of Study 0116.**

**Gilead will attempt to provide clinical study reports and data sets by Nov 10 from the first IA of study 116 and subsequent analysis and datasets will be provided when available. Gilead to provide a schedule of future data submissions.**

**Agency recommends a proposal for an EAP and to resubmit BTDR for the updated data on CLL.**

**2.1. Additional Comments**

Please clarify how multiplicity will be adjusted for testing secondary endpoints if the study were stopped early due to superiority at one of the interim analyses. Testing the secondary endpoints at the overall desired two-sided significance level of 0.05 whenever the PFS reaches statistical significance (interim or final analysis) will inflate the strong study-wise type I error rate. For further information see the reference: H. M. James Hung, Sue-Jane Wang, Robert O'Neill. Statistical Considerations for Testing Multiple Endpoints in Group Sequential or Adaptive Clinical Trials *Journal of Biopharmaceutical Statistics*, 17: 1201–1210, 2007.

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

/s/  
-----

AMY C BAIRD  
04/10/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 205858 and NDA 206545

**LATE-CYCLE MEETING MINUTES**

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

Dear Ms. Cutler:

Please refer to your New Drug Applications (NDAs) dated September 11, 2013 and December 6, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zydelig<sup>®</sup> (idelalisib) tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 5, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

R. Angelo de Claro, MD  
Clinical Team Lead  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** June 5, 2014 2:00 PM – 3:00 PM  
**Meeting Location:** White Oak Building #22, Room 1311

**Application Number:** NDA 205858 and NDA 206545  
**Product Name:** Zydelig<sup>®</sup> (idelalisib)  
**Applicant Name:** Gilead Sciences, Inc.

**Meeting Chair:** R. Angelo de Claro  
**Meeting Recorder:** Mara Miller

**FDA ATTENDEES**

Office of Hematology and Oncology Products

Richard Pazdur, Director  
Tamy Kim, Associate Director of Regulatory Affairs

Division of Hematology Products

Ann Farrell, Director  
Edvardas Kaminskas, Deputy Director  
Robert Kane, Deputy Director for Safety  
Angelo de Claro, Clinical Team Lead  
Nicole Gormley, Clinical Reviewer  
Barry Miller, Clinical Reviewer  
Donna Przepiorka, Clinical Reviewer  
Diane Leaman, Safety Project Manager  
Patricia Garvey, Senior Regulatory Project Manager  
Rachel McMullen, Regulatory Project Manager  
Mara Miller, Senior Regulatory Project Manager

Division of Hematology Oncology Toxicology

Haleh Saber, Pharmacology/Toxicology Supervisor  
Ramadevi Gudi, Reviewer

Office of Clinical Pharmacology

Julie Bullock, Team Lead  
Stacy Shord, Clinical Pharmacology Reviewer  
Dhananjay Marathe, Pharmacometrics Reviewer

Office of New Drug Quality Assessment

Ali Al Hakim, Branch Chief  
Janice Brown, Team Lead

Debasis Ghosh, Reviewer  
Li Shan Hsieh, Reviewer

Office of Biostatistics

Yuan-Li Shen, Team Lead  
Lei Nie, Team Lead  
Kyung Yul Lee, Reviewer  
Sirisha Mushti, Reviewer

Office of Surveillance and Epidemiology

Cynthia LaCivita, Acting Division Director, DRISK  
Naomi Redd, Risk Management Analyst, DRISK  
Shelly Harris, REMS Assessment Analyst, DRISK  
Tracy Salaam, Team Lead, DPV  
Wana Manitpisitkul, Safety Evaluator, DPV  
Kira Leishear, Epidemiologist, DEPI  
Peter Waldron, Medical Officer, DPV  
Joan Blair, Health Communications Analyst, DRIKS

Division of Medical Policy Programs

Nathan Caulk, Patient Labeling Reviewer

Office of Prescription Drug Promotion

Kathleen Davis, Reviewer

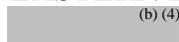
Office of Strategic Programs

Kim Taylor, Operations Research Analyst

Office of Manufacturing and Product Quality

Vipul Dholakia, Consumer Safety Officer

**EASTERN RESEARCH GROUP ATTENDEES**

 <sup>(b) (4)</sup> Independent Assessor

**APPLICANT ATTENDEES**

John McHutchison, EVP, Clinical Research  
Roger Dansey, VP, Clinical Research  
Lyndah Dreiling, Senior Director, Clinical Research  
Tobias Peschel, VP Drug Safety and Public Health (DSPH)  
Christopher Aguilar, Associate Director, DSPH  
Xiaoming Li, Director, Biostatistics  
Srinivasan Ramanathan, Director, Clinical Pharmacology  
Jennifer Stephens, Director, Regulatory Affairs  
Lauren Cutler, Manager, Regulatory Affairs  
Mike Kernan, Senior Director, Analytical Development  
Jason Chamberlain, Senior Research Scientist, Drug Safety Evaluation

## 1.0 BACKGROUND

NDA 205858 was submitted on September 11, 2013 and NDA 206545 was submitted on December 6, 2013 for Zydelig<sup>®</sup> (idelalisib).

Applicant's Proposed indication(s):

- Treatment of patients with chronic lymphocytic leukemia
- Treatment of patients with indolent B-cell Non-Hodgkin lymphoma

PDUFA goal date: NDA 205858: September 11, 2014  
NDA 206545: August 6, 2014

FDA issued a Background Package in preparation for this meeting on May 22, 2014.

## 2.0 DISCUSSION

### 1. Introductory Comments

#### **Discussion**

The FDA updated Gilead on the status of the review of both applications:

- Primary reviews are complete.
- Negotiations continue on the PMRs.
- FDA will send the revised Prescribing Information (PI) to Gilead by June 13, followed by the Medication Guide.
- REMS discussions will continue after the PI is complete.

### 2. Discussion of Substantive Review Issues

#### **Safety Issues**

DHP is concerned with the occurrence of the following serious and life-threatening toxicities in Zydelig-treated patients and recommends the following measures to the Applicant:

- a. addition of Boxed Warning for hepatotoxicity, gastrointestinal perforation, colitis, and pneumonitis
- b. submission of a Medication Guide
- c. addition of severe cutaneous reactions to Warnings and Precautions
- d. submission of a REMS communication plan to address Boxed Warning safety issues

#### **Discussion**

The FDA reiterated that safety issues would be handled through labeling, REMS and PMRs. The FDA continues to review the data in the application to finalize the PI.

### 3. Information Requests

Refer to information request sent on May 22, 2014 regarding request for submission of REMS materials and updated version of the prescribing information. Prescribing information should include more details on the frequency, severity, presenting signs and symptoms, outcomes, and management of the toxicities.

#### **Discussion**

There are currently no pending information requests.

### 4. REMS or Other Risk Management Actions

#### **Discussion**

REMS discussions will continue after the PI is complete in order to align the REMS and the PI. The FDA will send feedback on the REMS upon finalization of the PI. The FDA will need revised mock-ups when Gilead sends REMS revisions.

### 5. Major Labeling Issues

Given safety issues identified with Zydelig, DHP requests discussion with the Applicant regarding identification of patient population(s) most appropriate for treatment with Zydelig.

#### **Discussion**

The FDA stated that they will provide feedback in next iteration of the PI regarding concerns with endpoints. There are too few numbers for some of the requested specific indications.

FDA is recommending the accelerated approval pathway for the FL and SLL indications. Gilead has several randomized trials in progress that can be used to fulfill Subpart H (accelerated approval) requirements. The FDA stated that multiple trials may be listed as confirmatory trials. The terms for conversion to regular approval will be stated in the action letter.

The FDA stated that there is no problem verifying the PFS effect for the CLL indication. The FDA is still working on the wording of the indication and stated that generally the indications reflect the populations that were studied in the clinical trial. Gilead will provide the FDA with some suggested wording for the indication.

### 6. Postmarketing Requirements/Postmarketing Commitments

DHP recommends the following safety post-marketing requirements:

- a) Five-year safety follow-up for iNHL and CLL trials
- b) Evaluate safety of alternative dosing regimens for treatment durations 6 months or greater
- c) Conduct a study to characterize the incidence, diagnosis, and effective treatment of pneumonitis in idelalisib-treated patients

**Discussion**

Gilead stated that their trials are written as open ended, therefore, 5 year follow up for the trials is acceptable. Gilead also accepts the recommendation to provide interim reports with 3-year follow-up information.

The FDA reiterated concerns that the number of patients exposed greater than 6 months is small, and recommended consideration of alternative dosing regimens. FDA stated that PK sampling would be helpful with these trials.

[REDACTED] (b) (4)

The FDA and Gilead had discussion regarding pneumonitis. The FDA stated that this safety event is the least defined and it is still under discussion. The FDA will inform Gilead if both an observational and clinical trial are needed.

7. Wrap-up and Action Items

**Discussion**

The FDA is proceeding with final reviews. If approval action is taken, [REDACTED] (b) (4) bursts will be sent to Gilead for review. The press release will not be sent to Gilead for review.

**Action Items**

- The FDA will send the PI to Gilead next week, followed by the Medication Guide.
- Gilead will send a summary of the status of patients who are receiving treatment at dose levels of 300 mg BID.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/  
-----

ROMEO A DE CLARO  
06/17/2014



NDA 205858 and 206545

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zydelig (idelalisib) tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 5, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** June 5, 2014, 2:00 -3:00 PM EST  
**Meeting Location:** White Oak Building #22, Room 1311

**Application Number:** NDA 205858 and NDA 206545  
**Product Name:** Zydelig (idelalisib)  
**Indication:** Relapsed follicular B-cell non-Hodgkin lymphoma (FL); Relapsed small lymphocytic lymphoma (SLL); and Relapsed chronic lymphocytic leukemia (CLL)  
**Sponsor/Applicant Name:** Gilead Sciences, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

In addition to the contents of this background document, please refer to the following Discipline Review letters already provided to you:

NDA 205858, dated May 20, 2014  
NDA 206545, dated May 20, 2014

## **2. Substantive Review Issues**

The following substantive review issues have been identified to date:

See Discipline Review letters dated May 20, 2014.

### **Safety Issues**

DHP is concerned with the occurrence of the following serious and life-threatening toxicities in Zydelig-treated patients and recommends the following measures to the Applicant:

1. addition of Boxed Warning for hepatotoxicity, gastrointestinal perforation, colitis, and pneumonitis
2. submission of a Medication Guide
3. addition of severe cutaneous reactions to Warnings and Precautions
4. submission of a REMS communication plan to address Boxed Warning safety issues

### **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

### **REMS OR OTHER RISK MANAGEMENT ACTIONS**

The proposed outline of the REMS document submitted is acceptable, however the submission is incomplete. These additional items must also be submitted:

1. MS Word versions of all REMS materials (REMS Letters, Factsheet, Journal Information Piece, and REMS Website landing page), the REMS document, and a REMS Supporting Document.
2. Mock-up versions of all REMS materials. These may be submitted in Adobe pdf formats.
3. Include a proposed assessment plan of the REMS in the REMS Supporting Document.

Note that all of the risks outlined in the REMS and REMS materials must align with labeling. Revisions to the proposed documents are likely.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

## **LCM AGENDA**

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

### 2. Discussion of Substantive Review Issues – 15 minutes

#### **Safety Issues**

DHP is concerned with the occurrence of the following serious and life-threatening toxicities in Zydelig-treated patients and recommends the following measures to the Applicant:

- a. addition of Boxed Warning for hepatotoxicity, gastrointestinal perforation, colitis, and pneumonitis
- b. submission of a Medication Guide
- c. addition of severe cutaneous reactions to Warnings and Precautions
- d. submission of a REMS communication plan to address Boxed Warning safety issues

### 3. Information Requests – 5 minutes

Refer to information request sent on May 22, 2014 regarding request for submission of REMS materials and updated version of the prescribing information. Prescribing information should include more details on the frequency, severity, presenting signs and symptoms, outcomes, and management of the toxicities.

### 4. REMS or Other Risk Management Actions – 10 minutes

### 5. Major Labeling Issues – 10 minutes

Given safety issues identified with Zydelig, DHP requests discussion with the Applicant regarding identification of patient population(s) most appropriate for treatment with Zydelig.

### 6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

DHP recommends the following safety post-marketing requirements:

- a) Five-year safety follow-up for iNHL and CLL trials
- b) Evaluate safety of alternative dosing regimens for treatment durations 6 months or greater
- c) Conduct a study to characterize the incidence, diagnosis, and effective treatment of pneumonitis in idelalisib-treated patients

7. Wrap-up and Action Items – 5 minutes

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

/s/  
-----

ANN T FARRELL  
05/22/2014