

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205858Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205858

SUPPL #

HFD # 161

Trade Name Zydelig

Generic Name Idelalisib

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known 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 206545, 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:

(b) For each investigation not carried out under an IND or for which the applicant was not

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#: 205858

Supplement Number: _____

NDA Supplement Type (e.g. SE5): 1

Division Name: DHP

PDUFA Goal Date:

Stamp Date: 9/11/2013

September 11, 2014

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

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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<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**

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

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 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.

* 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

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

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 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 ^Δ
<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) 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
<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

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 205858

Supplement Number: _____

NDA Supplement Type (e.g. SE5): 1

Division Name: DHP

PDUFA Goal Date:

Stamp Date: 9/11/2013

September 11, 2014

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 small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies..

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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<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**

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

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 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.

* 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

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

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 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 ^Δ
<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) 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 †
				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.

* 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 ¹		
NDA # 205858 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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><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"> Proposed action User Fee Goal Date is <u>September 11, 2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input checked="" type="checkbox"/> Received
❖ Application Characteristics ³		

¹ 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.

² 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).

³ 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 type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input 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 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 – ^{(b) (4)} 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.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ 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): Accelerated Approval – 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"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included July 21, 2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included September 11, 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"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included July 21, 2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included September 11, 2013; February 21, 2014
❖ Labels (full color 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"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included July 15, 2014
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	October 3, 2013 October 1, 2013
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: November 5, 2013 DMEPA: October 31, 2013 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 ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	November 8, 2013
❖ 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 July 23, 2014
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> 	Pediatric Page- July 22, 2014
❖ 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>)	July 21(3), 18, 17, 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
❖ 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)	
❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A July 1, 2013 <input checked="" type="checkbox"/> No mtg February 25, 2014 June 5, 2014 N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	July 22, 2014
Division Director Summary Review (<i>indicate date for each review</i>)	July 15, 2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	July 7, 2014
PMR/PMC Development Templates (<i>indicate total number</i>)	July 18, 2014 (9 templates)
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review Co-signed May 9, 2014 review Review: May 9, 2014 Filing: November 5, 2013 <input checked="" type="checkbox"/> None

❖ 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>)	See page 94 of Clinical Review dated May 9, 2014
❖ 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"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	July 22, 2014; May 30, 2014; May 28, 2014 July 22, 2014 July 21, 2014; June 27, 2014; May 20, 2014
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	May 14, 2014; April 15, 2014; April 10, 2014
Clinical Microbiology <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
Biostatistics <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 9, 2014 Review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Co-signed May 9, 2014 Review
Statistical Review(s) (<i>indicate date for each review</i>)	Review: May 9, 2014 Filing: October 18, 2013
Clinical Pharmacology <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: October 30, 2013
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	April 18, 2014
• Supervisory Review(s) (<i>indicate date for each review</i>)	May 01, 2014 April 17, 2014 Co-signed April 3, 2014 Review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Review: April 3, 2014 Filing: September 27, 2013
❖ 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
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	May 13, 2014
• 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 9, 2014 Biopharm Filing: October 16, 2013 Filing: October 7, 2013
❖ Microbiology Reviews	
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	Review: January 2, 2014 Filing: September 25, 2013
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> CGMP/Facilities Filing Review: March 21, 2014
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See May 12, 2014 Product Quality Review, Page 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>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: May 17, 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 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ 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]
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 (b) (4) 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

From: Miller, Mara Bauman [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.cutler@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 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 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.

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/s/

MARA B MILLER
07/21/2014

From: Miller, Mara Bauman
To: 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
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immediately following this page

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/s/

MARA B MILLER
07/21/2014

From: Miller, Mara Bauman
To: 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
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/s/

MARA B MILLER
07/18/2014



Naumann Chaudry, Pharm.D.
Director, Regulatory Affairs Advertising and Promotion
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

RE: NDA #205858
ZYDELIG™ (idelalisib) tablets, for oral use
MA #1

Dear Dr. Chaudry:

This letter responds to Gilead Sciences, Inc.'s (Gilead) July 14, 2014, letter to the Office of Prescription Drug Promotion (OPDP) requesting advisory comments on proposed core launch promotional materials for ZYDELIG™ (idelalisib) tablets for oral use (Zydelig). This material was submitted pursuant to subpart H regulations CFR 314.550. This submission includes the following materials:

- **HCP Journal Ad (GILP0220)**
- **Zydelig Approval Press Release**

OPDP has reviewed the proposed professional launch promotional materials listed above and offers the following comments, which should be applied to all current and future promotional materials that contain the same or similar claims or presentations for Zydelig. Please note that these comments reflect the draft product labeling (PI) sent to Gilead on July 11, 2014. These comments are tentative pending finalization of the Zydelig PI. All promotional materials for Zydelig should be updated to reflect the final PI approved by the FDA.

(b) (4)

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/s/

KATHLEEN T DAVIS
07/17/2014

From: Miller, Mara Bauman
To: 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
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/s/

MARA B MILLER
07/17/2014

From: Miller, Mara Bauman
To: 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
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/s/

MARA B MILLER
07/17/2014

From: Miller, Mara Bauman
To: 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
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/s/

MARA B MILLER
07/17/2014

From: Miller, Mara Bauman
To: 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
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/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 and via electronic gateway submission by **Wednesday, July 2nd, 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 17th, 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 and the DHCP letters and DPS letters refer to 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). 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 | 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 and via electronic gateway submission by **Wednesday, July 2nd**.

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 17th, 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 and the DHCP letters and DPS letters refer to 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). 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
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MARA B MILLER
06/30/2014

From: Miller, Mara Bauman
To: 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
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MARA B MILLER
06/13/2014

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858 PMR Discussions
Date: Tuesday, June 03, 2014 1:22:00 PM
Attachments: [NDA205858_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)

NDA 205858 Post Marketing Requirements

A. PMR Zydelig iNHL Subpart H dose finding trial

PMR Description:

Design, conduct, and provide the full study report and data sets of a dose-finding trial that optimizes safety and efficacy of chronic administration of idelalisib in patients with indolent lymphomas. Include adequate PK sampling to provide dose-response data (for efficacy and safety)

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

B. PMR Zydelig iNHL Subpart H trial 0124

PMR Description: Submit the complete study report and data showing clinical efficacy and safety from study GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.

PMR Schedule Milestones:	Final Protocol Submission:	<u>completed</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

C. PMR Zydelig iNHL Subpart H trial 0125

PMR/PMC Description: Submit the complete study report and data showing clinical efficacy and safety from study GS-US-313-0125 Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated iNHL

PMR Schedule Milestones:	Final Protocol Submission:	<u>completed</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

D. Safety PMR Zydelig iNHL pulmonary toxicity

PMR Description: Conduct a clinical study to characterize the incidence, diagnosis and effective treatment of idelalisib-related pneumonitis. Pool data from all relevant trials to characterize this risk.

NDA 205858 Post Marketing Requirements

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

E. Safety PMR Zydelig iNHL trial 101 99

PMR Description: Provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete study report and data showing long-term safety with 5 years of follow-up from study 101-99 Phase 1/2 extension study of safety and durability of idelalisib in hematologic malignancies

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>MM/YYYY</u>
	Interim Report Submission (3-year follow-up)	<u>MM/YYYY</u>
	Final Report Submission (5-year follow-up):	<u>MM/YYYY</u>

F. Safety PMR Zydelig iNHL trial 0124

PMR Description: Provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete study report and data showing long-term safety with 5 years of follow-up from study GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>MM/YYYY</u>
	Interim Report Submission (3-year follow-up)	<u>MM/YYYY</u>
	Final Report Submission (5-year follow-up):	<u>MM/YYYY</u>

G. Safety PMR Zydelig iNHL trial 0125

PMR Description: Provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with other agents such as bendamustine (B) and rituximab (R). Submit the complete study report and data showing long-term safety with 5 years of follow-up from study GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination

NDA 205858 Post Marketing Requirements

with BR in subjects with previously treated iNHL

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>MM/YYYY</u>
	Interim Report Submission (3-year follow-up):	<u>MM/YYYY</u>
	Final Report Submission (5-year follow-up):	<u>MM/YYYY</u>

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/s/

MARA B MILLER
06/03/2014

From: Miller, Mara Bauman
To: 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" 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)

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/s/

MARA B MILLER
05/22/2014



NDA 205858

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 September 11, 2013, received September 11, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zydelig[®] (idelalisib) Tablets.

During the review of your application, we have identified the following deficiencies:

CLINICAL

1.  (b) (4)
2. 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 monotherapy with at least 5 years of follow-up.
3. Your safety data includes cases of severe or life-threatening pneumonitis with an infectious etiology and that were treated with corticosteroids. A noninfectious etiology was supported by biopsies. Your proposed labeling indicates uncertainty about the occurrence of drug-induced pneumonitis in patients treated with Zydelig. You will need to conduct a study to characterize the incidence, diagnosis and effective management pneumonitis arising in the setting of Zydelig therapy.
4. 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.

5. 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.
6. Your proposed labeling indicates that severe diarrhea due to Zydelig resolved with drug interruption and additional treatment such as enteric budesonide. You will need to provide data showing that enteric budesonide 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 Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROMEO A DE CLARO
05/20/2014

From: Miller, Mara Bauman
To: 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)

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/s/

MARA B MILLER
05/14/2014

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)

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/s/

MONSURAT O AKINSANYA
04/18/2014

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 ≥ 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 ≥ 8 weeks, while the Imaging Charter states in section 13.5.7 that PR will be based on a change in disease status meeting ≥ 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 ≥ 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)

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/s/

MONSURAT O AKINSANYA
04/18/2014

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Monday, April 14, 2014 4:53 PM
To: lauren.cutler@gilead.com
Cc: Miller, Mara Bauman; Akinsanya, Lara
Subject: Pharmacology/Toxicology Information Request for NDA 205858

Dear Lauren Cutler,

Please respond to the below information request from our nonclinical team:

It is unclear how you calculated the safety margins in your labeling changes for the nonclinical sections. Below is the list of Animal studies we used with corresponding doses and AUCs for the nonclinical sections of the label. Please provide the human AUC value(s) (indicate the time-point; i.e. AUC₀₋₂₄ or AUC₀₋₁₂) and the exposure ratios. If you used a different animal study/dose, indicate the study number, the dose, and the associated AUC by adding rows to the table or by using the track change function.

(b) (4)

Please provide this information by **COB on Wednesday, 4/16/2014.**

Thank you
Lara Akinsanya for Mara Miller

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)

APPEARS THIS WAY ON ORIGINAL



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/s/

MONSURAT O AKINSANYA
04/14/2014



NDA 205858

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 have the following comments regarding your drug container label. Please provide a response by April 7, 2014.

Drug container label for 100 mg and 150 mg bottles:

- a. Both strengths use (b) (4) color for the boxes around the strength and the bar at the bottom of the container label. This can contribute to the selection of the wrong strength errors. Thus, please provide sufficient differentiation between the two strengths of the product by using different colors to highlight the strengths and to highlight the bar at the bottom of the label.
- b. Bold the statement "Dispense only in original container".
- c. Debold the statement "Rx Only".
- d. Re-orientate the barcode to a vertical position to improve scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature if the bottle is round in shape.
- e. Add the statement "Keep this and all medications out of the reach of children" on the side panel.

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

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/s/

MARA B MILLER
04/01/2014

From: Miller, Mara Bauman
To: 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

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/s/

MARA B MILLER
03/28/2014

From: Martin, Jewell
To: ["Lauren Cutler"](#)
Cc: [Agosto, Teicher](#)
Subject: NDA 205858 Information Request
Date: Wednesday, March 19, 2014 11:20:00 AM

Ms. Cutler,

Please see the following CMC information request below. A written response is requested by March 24, 2014.

- We do agree with your current proposal to retain PAR in Section 3.2.S.2.6. To further clarify your comment, include the following statement as a footnote to Table 19, 22-25 and submit the revised Section 3.2.S.2.6: *"The PARs are presented for informational purposes only, and not to justify operation outside of the NORs."*

- With limited batch data, your proposed plan to (b) (4)

(b) (4) However, the adequacy of such information is a review issue.

- Your proposed plan to exclude (b) (4) as a release test for drug substance appears to be rational. Provide a comprehensive tabular summary of control strategy to (b) (4)

In addition to formally submitting your response to your NDA, please send me a courtesy copy via email.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625

10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov



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/s/

JEWELL D MARTIN
03/19/2014

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858- Information Request
Date: Monday, March 10, 2014 9:49:00 AM
Importance: High

Hello Lauren,

We have the following information request for NDA 205858. Please provide a response **as soon as possible.**

- CAL-102 was used in the hERG assay (study number BHR00004). Please provide the information on the relevance and relationship of CAL-102 to Cal-101.

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
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/s/

MARA B MILLER
03/10/2014



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

Patrick J. Zhou, Independent Assessor
Uche Chimeh, 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%) (b) (4)
- 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 (b) (4) 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.

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/s/

ROMEO A DE CLARO
03/06/2014



NDA 205858

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 the Quality section of your submission and have the following comments and information requests. We request a written response by COB March 12, 2014, in order to continue our evaluation of your NDA.

1. Your proposed Proven Acceptable Ranges (PAR) provided in Table 19, 22-25 of Sec 3.2.S.2.6 are not supported by adequate data including, but not limited to, DOE studies and scale up changes. The proposed PAR values are not acceptable as submitted. We recommend that you remove the PAR column from the above Tables and use Normal Operating Ranges (NORs) and set points only for the process parameters for manufacturing, (b) (4) and (b) (4) procedures. Also, revise (b) (4) of idelalisib as described in Sec 3.2.S.2.2 to reflect the above changes.
2. Your control strategy to (b) (4) is not adequate. We recommend that you should perform (b) (4) test as part of the drug substance release specification to ensure the purity of the product.
3. Since drug substance is a (b) (4) the control of (b) (4) quality should be reflected on drug substance release specification. Although, (b) (4) purity of (b) (4) starting material and data from several drug substance batches provide some assurance of quality control, it does not necessarily preclude the need for testing the identity or (b) (4) purity of final drug substance. We believe the risk of not testing a (b) (4) drug substance at release is high. We recommend that include a test for either (b) (4) identity or (b) (4) purity in drug substance specification.

4. Following comments were communicated to the applicant as filing review comments on 11/19/2013 (received no response as of the date of this IR)

- We do not agree with the designation of (b) (4) as a regulatory starting material (b) (4). Information provided in the submission does not establish that future changes in the proposed starting materials would not impact the quality of the drug substance. The starting material should be (b) (4). Earlier compounds (for example, (b) (4)) should be selected as the regulatory starting material.
- Section 3.2.S.2.2 describes (b) (4) and (b) (4) of (b) (4) and Idelalisib. Provide a tabular summary of (b) (4) and Idelalisib batches that were either (b) (4) or (b) (4) and the reason.

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/05/2014

From: Miller, Mara Bauman
To: 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)

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/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.

Recommended Acceptance criterion
$Q = \text{(b) (4)} \text{ in 20 min}$

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] ^{(b) (4)} in the ranges tested
4. Provide rationale for the high variability in dissolution profiles observed in the batches manufactured at the [REDACTED] ^{(b) (4)} (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

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/s/

MARA B MILLER
02/10/2014



NDA 205858

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 to request #1 by **Friday January 31, 2014** and a response to requests 2-11 by **February 24, 2014**.

1. We have reviewed your submission dated 12/23/2013 with the explanation regarding drug accountability and determination of drug exposure in the patients who received idelalisib monotherapy on protocols 02, 09, 10, 11 and 99. Please provide an integrated dataset showing a continuous record (including start date, end date and study day) of idelalisib dosing for all 352 subjects on monotherapy (101-02, 101-09, 101-10 and 101-11 and for those who continue on 101-99) from start of therapy to date off study.

This dataset will be used not only to describe exposure at various doses of idelalisib, but also to identify the actual dose on any given date of an adverse event, and to confirm that the dose modifications in the proposed labeling are appropriate.

To this end, the dataset should include the actual daily dose-schedule (i.e., 150 mg BID, 200 mg qD, etc) as prescribed for the period of interest rather than (b) (4). Occasional missed doses due to noncompliance are not relevant to these analyses, but you may include that information. You may impute the date of interruption of dosing based on pill count (e.g., 14 pills returned means dose=0 mg for the last 7 days of a BID dosing period) or on the date of onset of an adverse event if an exact date of drug interruption is not documented in the study record. Include in your submission the method of imputation used.

We recommend that you name this as an ISS ADAM dataset (e.g., ADEX) to be clear that it is derived.

2. The CSR for Protocol 101-09 include audit certificates for 6 clinical sites, but the report does not discuss the findings.
 - a) Please identify any substantial issues identified in your audits, what corrective actions were required, and whether implementation of the corrective actions was successful.
 - b) Please clarify whether Study Site 119 (Gopal, Seattle, WA) was the only site where returned study drug was destroyed before monitors could confirm the pill count.
3. Please provide clarification for the following observations about outcomes in the ISS dataset ADSL:
 - a) The cause of death for Subject 109-09020 is listed as progressive disease, but the subject was taken off study due to an adverse event, and there is no documentation of progressive disease in the submission. Please confirm the accuracy of the cause of death as listed and indicate where the documentation of progression is found.
 - b) The cause of death for Subject 504-09043 is listed as progressive disease, but the subject was taken off study by physician's opinion, and there is no documentation of progressive disease in the submission. Please confirm the accuracy of the cause of death as listed and indicate where the documentation of progression is found.
 - c) The cause of death for Subject 605-09083 is listed as progressive disease, but the subject was taken off study by physician's opinion, and there is no documentation of progressive disease in the submission. Please confirm the accuracy of the cause of death as listed and indicate where the documentation of progression is found.
 - d) The cause of death for Subject 119-09060 is listed as hypoxic respiratory failure, but the subject was taken off study for progressive disease. Please clarify whether the cause of death was an adverse drug reaction or progressive disease and indicate where the documentation of progression is found.
 - e) The cause of death for Subject 147-09016 is listed as toxoplasmosis, but the narrative indicates that the subject was improved with treatment. Please clarify the cause of death and indicate where the documentation of recurrence of toxoplasmosis is found.
 - f) The cause of death for Subject 149-09104 is listed as pneumonia. The narrative indicates that cultures and other diagnostic tests were performed, but there is no follow-up reported. Please clarify the cause of pneumonia in this subject and indicate where the documentation of progression is found.

4. Please confirm that you have no studies of anti-drug antibodies in humans.
5. Please clarify whether you have any information of lymphocyte subsets (e.g., CD19+ lymphocytes, CD4+ lymphocytes) in subjects treated with idelalisib monotherapy.
6. In the 146 INHL patients treated with idelalisib 150 mg BID x 28 days, the incidence of any grade diarrhea/colitis was 58% in users of proton pump inhibitors (PPI) vs 36% in nonusers. Please clarify whether the increased incidence in PPI users represents a drug-drug interaction or an additive effect due to the overlapping adverse event profile of PPIs and idelalisib.
7. Nine of the 352 subjects treated with idelalisib monotherapy were identified as having second malignancies. We have the following questions about these subjects;
 - a) Please provide a narrative addressing the squamous cell carcinoma reported for subject 2514-103802 on protocol 1101-02.
 - b) Please provide a narrative addressing the squamous cell carcinoma of the skin reported for subject 119-09004 on protocol 1101-09.
 - c) Please clarify if the rate of squamous cell carcinoma is higher than expected for this population.
 - d) Please clarify if the rate of myelodysplastic syndrome is higher than expected for this population.
8. The narratives provided in the application occasionally described results of organ biopsies performed in the course of evaluation of adverse events. Please provide copies of the results of biopsies of lung, skin, GI tract or liver from any of the 352 subjects treated with idelalisib monotherapy.
9. There is a high rate of infectious pneumonias in the subjects treated with idelalisib. Please clarify if the risk of pneumonia is related to the occurrence of hypogammaglobulinemia.
10. The safety assessment showed a substantial number of opportunistic infections (i.e., PCP, CMV) that usually occur in patients with T-cell immunodeficiencies. Please clarify whether idelalisib or its major metabolite inhibits T-cell function.
11. In Protocol GS-US-313-0130, there was an increase in the incidence of idelalisib-related adverse events when subjects received idelalisib concurrent with digoxin. Your report noted that idelalisib had no effect on the PK of digoxin. Please clarify if digoxin altered the PK of idelalisib, or whether the increase in adverse events was due to the duration of idelalisib use by the study subjects rather than an interaction with digoxin.

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

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/s/

MARA B MILLER
01/27/2014

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858, Information Request
Date: Thursday, January 09, 2014 10:44:00 AM
Importance: High

Hello Lauren,

Regarding NDA 205858, we have the following information request. Please provide a response by COB on Thursday January 16, 2014.

Idelalisib demonstrates pH dependent solubility and the estimated concentration in the gastrointestinal tract appears higher than the solubility at a pH that is anticipated with drugs that elevate gastric pH. Provide analysis and associated codes and datasets of the effects of [patients who received concomitant](#) histamine 2 receptor antagonists, proton pump inhibitors or antacids on

- a. The observed and population pharmacokinetic estimated minimal plasma concentrations (C_{trough}) and the population pharmacokinetic estimated maximal plasma concentrations (C_{max}) and area under the concentration-time curve (AUC),
- b. On safety events using the integrated summary of safety, and
- c. Efficacy as determined in Study 101-09 for iNHL and in Study GS-US-312-0116 for CLL.

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)

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/s/

MARA B MILLER
01/09/2014

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858 Information Request
Date: Tuesday, January 07, 2014 1:57:00 PM
Importance: High

Hello Lauren,

Regarding NDA 205858, we have the following information requests. Please provide a response on Thursday January 9, 2014.

Original Information Request: For study 101-02, provide a SAS transport file that lists all pharmacokinetic parameters estimated for each individual patient.

Gilead Response: The SAS transport file that lists the PK parameters estimated for each individual patient enrolled in Study 101-02, based on the Pop-PK model, was provided in dataset [adidela.xpt](#) which was submitted on Sep 11, 2013 (Seq 0000).

Modified Information Request: For Study 101-02, provide codes and SAS transport file that includes all pharmacokinetic parameters from observation and NCA for each individual **for days 1 and day 28**, including CMIN, CMAX, AUC, HALF-LIFE and TMAX **that can be used** to reproduce tables and figures included in report summarizing the PK of IDELA for Study 101-02, **entitled [Pharmacokinetic Parameters for Study 101-02](#)**, presented in Appendix 16.1.10 of the study report.

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)

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/s/

MARA B MILLER
01/09/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, January 02, 2014 2:01 PM
To: 'lauren.cutler@gilead.com'; 'jennifer.stephens@gilead.com'
Cc: Miller, Mara Bauman
Subject: NDA 205858 - Information Request

Importance: High

Hello,

Please refer to your NDA 205858, we have the following information request. Please provide a response by **3pm (EST) Friday January 3, 2014.**

- 1. Please clarify the discrepancy we've identified regarding dose modifications in the EX and ADSL datasets. Forty-five [42 in EX; 45 in ADSL] patients enrolled in Study 101-09 had dose reductions from the starting dose: 40 [EX and ADSL] patients had their dose reduced to 100 mg BID and 5 patients [2 in EX; 5 in ADSL] had their dose reduced to 75 mg BID. Of the 40 patients who had their dose reduced to 100 mg BID, 7 [8 in EX; 7 in ADSL] patients had their dose further reduced to 75 mg BID.*

Please officially submit the responses to NDA 205858 and also e-mail to me and Mara Miller.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
01/02/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, January 02, 2014 3:01 PM
To: lauren.cutler@gilead.com; jennifer.stephens@gilead.com
Cc: Miller, Mara Bauman
Subject: NDA 205858 - Information Request #2

Importance: High

Hello,

Please refer to your NDA 205858, we have the following information request. Please provide a response by **4pm (EST) Monday January 6, 2014.**

1. Provide a table that lists which formulation was used in each trial included in the new drug application. Reference which studies used the "to-be-marketed" tablet formulation (as compared to earlier tablet formulations) and which studies used the formulations included in the relative bioavailability study 101-06.
2. Provide criteria and methodology used to determine 17p deletion, TP53 mutation and immunoglobulin heavy chain mutation positivity for Studies 312-0116, 101-02 and 101-08.
3. For study 101-09, clarify if the parameter exstdy in the ex.xpt file is the first day of the reduced dose.
4. For study 101-02, provide a SAS transport file that lists all pharmacokinetic parameters estimated for each individual patient.

Please officially submit the responses to NDA 205858 and also e-mail to me and Mara Miller.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
01/02/2014

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com; Jennifer.Stephens@gilead.com
Subject: NDA 205858 Information Request
Date: Friday, December 27, 2013 2:27:00 PM
Importance: High

Hello Lauren,

Regarding NDA 205858, we have the following information request. Please provide a response by COB Friday January 3, 2014:

- In your submission dated 12/20/2013, you indicated that there was an error on the slides prepared for the Application Orientation Meeting, and that there were 281 rather than 278 subjects in the healthy volunteer studies. In the integrated dataset included in that submission, we identified 300 subjects exposed to a study agent as listed in ex.xpt and sv.xpt, but other datasets (such as adlb.xpt and adsl.xpt) have data for only 281 subjects. We have reviewed the clinical study reports for all 11 healthy volunteer studies, and we noted that the sum of exposed subjects in those reports is 300. Please provide corrected integrated datasets for the 11 healthy volunteer studies, including all requested data for all 300 subjects.

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)

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/s/

MARA B MILLER
12/27/2013

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858 Information Request
Date: Tuesday, December 17, 2013 3:31:00 PM
Importance: High

Hello Lauren,

Regarding NDA 205858, we have the following information request. Please provide a response by Friday December 20, 2013.

- We are unable to determine idelalisib exposure from the integrated dataset ex.xpt for the NHL indication. The file appears to be a dispense list rather than a record of medications taken. Please clarify what dataset shows a continuous record of the doses taken or when treatment was modified or interrupted for each subject. If there is no such dataset, please provide an integrated dataset showing such a record of idelalisib dosing for all subjects on monotherapy (101-02, 101-09, 101-10, 101-11 and 101-99).

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
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/s/

MARA B MILLER
12/17/2013



NDA 205858

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.

- *We are unable to find bone marrow assessment results on 6 of the 7 patients with complete responses. Please provide or direct us to the information for the following subjects on protocol 101-09 by **December 6, 2013**:*
 - 111-09031*
 - 111-09032*
 - 117-09023*
 - 121-09123*
 - 145-09074*
 - 152-09102*
- *Your application includes results from 11 individual studies with 278 healthy volunteers. We plan to perform an integrated analysis of safety in the healthy volunteer population. Please send integrated datasets for the healthy volunteers that include all information on demographics, prior medical history, exposure, concomitant medications, comments, study visits, adverse events, clinical laboratory tests, and vital signs. Please also submit narratives of any serious adverse events in this population. Submit a response by **December 11, 2013**.*

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

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/s/

MARA B MILLER
11/27/2013



NDA 205858

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.

- *FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **Idelalisib NDA 205858** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.*

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

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/s/

MARA B MILLER
11/27/2013

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com
Subject: NDA 205858 Information Request
Date: Friday, November 22, 2013 2:48:00 PM
Attachments: [HighlightsofClinicalPharmacology.doc](#)

Hello Lauren,

Please complete the attached document and submit to the NDA as soon as possible.

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)

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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/s/

MARA B MILLER
11/22/2013



NDA 205858

**FILING COMMUNICATION -
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 September 11, 2013, received September 11, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zydelig (Idelalisib) 100 mg and 150 mg Tablets.

We have completed our filing review and have determined that your application for the proposed indication of refractory indolent non-Hodgkin lymphoma (iNHL) 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 **Standard**. 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 September 11, 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 23, 2014. In addition, the planned date for our internal mid-cycle review meeting is February 10, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application. However, we reserve the right to notify you in the future if there is a change in our plans.

During our filing review of your application, we identified the following potential review issues:

Product Quality

1. We do not agree with the designation of (b) (4) as a regulatory starting material (b) (4). Information provided in the submission does not establish that future changes in the proposed starting materials would not impact the quality of the drug substance. The starting material should be (b) (4).
Earlier compounds should be designated as the regulatory starting material.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Product Quality

1. Section 3.2.S.2.2 describes (b) (4) and (b) (4) of (b) (4) and Idelalisib. Provide a tabular summary of (b) (4) and Idelalisib batches that were either (b) (4) or (b) (4) and the reason.

Biopharmaceutics

1. Provide individual dissolution data for all the batches used to support the proposed acceptance criterion.
2. Provide dissolution profile comparisons in the proposed QC medium between the products manufactured at the (b) (4) (biobatch) and (b) (4) (commercial product). These data are needed to support the bridging between these two manufacturing sites.

Product Quality Microbiology

1. You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.
 - a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 - i. Define the maximum processing time for the (b) (4)
 - ii. Define the maximum holding time for the (b) (4)
 - b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria

established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

- c. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

- d. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.
2. Describe the sample prep for the 100 mg and 150 mg tablets used in the antimicrobial effectiveness test. The compendial test is a suspension test and not traditionally conducted for solid dosage forms.
3. Define the batch(es) used for (b) (4) activity testing. Provide the storage conditions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (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) 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) 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 product for the proposed 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

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/s/

ANN T FARRELL
11/19/2013



NDA 205858

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. We request a prompt written response in order to continue our evaluation of your NDA.

- Please provide the following items along with the population PK and exposure-response reports that you are going to provide on 12/13/2013 as stated in your amendment letter dated 11/08/2013:
 - The analysis datasets (including input and output files/tables for final Population-PK model) and associated codes to reproduce the results in Population-PK report and Exposure-response analyses for CLL.
 - Refer to the following pharmacometric data and models submission guidelines for your submission:
(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>)

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

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/s/

MARA B MILLER
11/13/2013

From: Miller, Mara Bauman
To: lauren.cutler@gilead.com; Jennifer.Stephens@gilead.com
Subject: NDA 205858, IR
Date: Thursday, November 07, 2013 5:02:00 PM
Importance: High

Hello Lauren and Jennifer,

As discussed during our teleconference, we are providing you with a list requested items. Submit a submission plan by 12pm EST, 11/8/13 (Friday), regarding all the additional submissions to support the CLL indication.

1. Module 2 must be updated with information relevant to the CLL indication.
2. The analysis data sets were not included in the submission.
3. The exposure dataset, ex.xpt, contained the following deficiencies:
 - The start date of treatment and end date of treatment for each row are based on study visit, and do not provide information about drug administered during the intervening time period
 - The exposure dataset should include information to allow assessment of treatment interruptions (p.26 of the SAP states: Duration of exposure to IDELA/placebo will be defined as (min(last IDELA/placebo dosing date[ie, captured on study drug completion CRF page], data cutoff date) – first IDELA/placebo dosing date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in months. Submit detailed exposure information that accounts for all study drugs received, including actual doses on all treatment days for all patients.
 - The dataset should contain un-blinded data for ease of analysis
4. The tabulation datasets do not contain information for all subjects in the ITT population. For example, in the response data set, rs.xpt, information for 181 subjects is included. It is understood that a portion of subjects did not have post-baseline assessments performed, but their information should still be included in the datasets. Submit the raw datasets for efficacy that includes data for all the patients in the ITT population (N=220).

In order to consider the above information for filing of the iNHL application, you must address all of the above deficiencies by 12pm EST, 11/9/13 (Saturday).

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)

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/s/

MARA B MILLER
11/13/2013



NDA 205858

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. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide the human AUC at the recommended labeling dose of 150 mg BID of Idelalisib.

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

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/s/

MARA B MILLER
10/31/2013



NDA 205858

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 the Prescribing Information (PI) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit a revised PI by November 4, 2013.

1. All headings in Highlights must be **bolded**.
2. Product title in Highlights must be **bolded**.
3. Initial U.S. Approval in Highlights must be placed immediately beneath the product title.
4. Patient Counseling Information Statement must be **bolded**.
5. Revision date at end of highlights must be **bolded**.
6. Highlights/Adverse Reactions: Avoid the term "adverse event." Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in the highlights.
7. Full Prescribing Information: Section 6 - Adverse Reactions: Use the term "adverse reactions" rather than the terms "adverse event" and "treatment-emergent adverse events." Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in the labeling.
8. Full Prescribing Information: Section 7 - Drug Interactions: Use numbered subsection headings to organize the information (7.1, 7.2).
9. Full Prescribing Information: Section 17 - Patient Counseling Information: Numbered subsections are not recommended because they may be redundant with subsection headings elsewhere in the label. Organize information by subsection headings or bulleted items.
10. Full Prescribing Information: Section 17 - Patient Counseling Information: Revise the first statement to read "Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

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/s/

MARA B MILLER
10/28/2013



NDA 205858

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. We request a prompt written response in order to continue our evaluation of your NDA. Please submit a response by October 28, 2013.

1. Submit a dataset, as a SAS transport file (.xpt), with one site per row, the following information from clinical trial 312-0116. Include a define.pdf file.
 - Site number
 - Principal investigator
 - Location: Address, City, State, Country
 - Contact Information: Name, Phone, Fax, Email
 - Number of subjects screened
 - Number of subjects randomized (total and per arm)
 - Number of subjects treated (total and per arm)
 - Number of subjects who achieved CR or PR (total and per arm)
 - Number of subjects who achieved CR (total and per arm)
 - Number of subjects with PFS events (total and per arm)
 - Number of protocol violations (total, major, and minor) per arm
 - Number of deaths per arm
 - Number of subjects who experienced SAEs per arm
 - Number of subjects who discontinued due to AE per arm

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

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/s/

MARA B MILLER
10/21/2013



NDA 205858

**METHODS VALIDATION
MATERIALS RECEIVED**

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

Dear Lauren Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Idelalisib Tablets and to our October 7, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 17, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/18/2013



NDA 205858

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. We request a prompt written response in order to continue our evaluation of your NDA. Please submit a response to request #1 by **October 14, 2013** and a response to requests 2- 5 by **November 1, 2013**.

1. Provide a summary data file of treatment outcomes for protocol 101-09 in SAS transport format (.xpt). Include at least the following variables in this data file: study identification number, site identification number, subject number, date of start of treatment, best response, time to best response. Include disease subtype and all pertinent measures of disease response, e.g. lymph node, marrow, spleen, extranodal sites, spleen, liver. Also include patients from trials 101-02/99 with iNHL who received the proposed indication dose.
2. Provide a SAS transport file (.xpt) of protocol deviations. Include at least the following variables in this data file: study identification number, site identification number, subject number, treatment arm, protocol deviation or violation, comment, date, and study day.
3. Construct a table that delineates CRFs for each of these categories: deaths, serious adverse events, and dropouts due to adverse events.
4. Submit source documentation for refractory disease criteria by patient on trial 101-09.
5. Provide in SAS transport format (.xpt) a file that lists enrollment by site.
 - a. Clarify if you have used unique study site numbers across protocols (each study site gets one identifier, that identifier is used for all protocols in which the center participated, and no other center is identified by that number in any other

protocol). If the study site identifier is not unique, please assign a unique identifier for each site.

- b. In the enrollment data file, there should be a single row for each study site, and in addition to the unique site identifier, the variables for each site should include investigator name, city, country, number of enrolled subjects for each protocol and total enrollment at the site. Include the protocol site identifier for each protocol if a non-unique site number was used in the datasets in the Clinical Study Reports.

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

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/s/

MARA B MILLER
10/09/2013



NDA 205858

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. We request a prompt written response in order to continue our evaluation of your NDA. Please submit a response by **October 14, 2013**.

Submit a dataset as a SAS transport file (.xpt), with the following information from clinical trial 101-09, one site per row. Use lymphoma subtypes for the cohorts. Include a define.pdf file.

- Site number
- Principal investigator
- Location: Address, City, State, Country
- Contact Information: Name, Phone, Fax, Email
- Number of subjects screened (total and per cohort)
- Number of subjects enrolled (total and per cohort)
- Number of subjects treated (total and per cohort)
- Number of subjects who achieved CR or PR (total and per cohort)
- Number of subjects who achieved CR (total and per cohort)
- Number of protocol violations (total, major, and minor)
- Number of deaths
- Number of subjects who experienced SAEs
- Number of subjects who discontinued due to AE

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

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/s/

MARA B MILLER
10/09/2013



NDA 205858

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Gilead Sciences, Inc.
Attention: Lauren Cutler, MS, RAC
Manager, Regulatory Affairs
199 East Blaine Street
Seattle, WA 98102
FAX: (206) 728-5095

Dear Lauren Cutler:

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

We will be performing methods validation studies on Idelalisib 100 and 150 mg tablets, as described in NDA 205858.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

- TM-212.00 Elemental Impurities in Idelalisib Drug Substance by (b) (4)
- TM-199.00 Identification, Assay and Impurities of Idelalisib Drug Substance by HPLC
- TM-211.00 Identification of Idelalisib Tablets by UV Spectrophotometry
- TM-205.00 Identification, Assay and Degradation Product Content of Idelalisib Tablets by HPLC

Samples and Reference Standards

- 2 x 1 g Idelalisib drug substance
- 2 x 200 mg Idelalisib drug reference standard
- 30 mg (b) (4)
- 30 mg (b) (4)
- 30 mg (b) (4)
- 100 Idelalisib 100 mg tablets
- 100 Idelalisib 150 mg tablets

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/07/2013



NDA 205858

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 tablets.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please provide a response by November 4, 2013.

1. Additional data sets are needed for the safety analysis. Please submit integrated datasets for the ISS population for the following domains:
 - a) Exposure (EX.XPT)
 - b) Concomitant medications (ADCM.XPT)
 - c) Comments (CO.XPT)
 - d) Study Visits (SV.XPT)
 - e) Performance status (ADPS.XPT)
 - f) Marrow results (ADBM.XPT)
 - g) Prior tumor history (ADDH.XPT)
 - h) Prior medical history (ADMH.XPT)

If you have any questions, call me at (301) 796-6083.

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

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/s/

MARA B MILLER
10/04/2013



NDA 205858

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Jennifer Stephens
Director, Regulatory Affairs

Dear Ms. Stephens:

Please refer to your New Drug Application (NDA) dated September 11, 2013, received September 11, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Idelalisib Tablets, 100 mg and 150 mg.

We also refer to your correspondence dated September 19, 2013, and received September 20, 2013, requesting review of your proposed proprietary name, Zydelig. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 20, 2013, 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 CDR 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 (301)796-0683.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/03/2013



NDA 205858

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: September 11, 2013

Date of Receipt: September 11, 2013

Our Reference Number: NDA 205858

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 November 10, 2013, 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. 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

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/s/

MARA B MILLER
09/13/2013



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 July 1, 2013. The purpose of the meeting was to discuss a proposed application in support of Idelalisib for the treatment of patients with indolent B-cell NHL (b) (4)

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 Amy Baird, Regulatory Project Manager at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, RN, MS, ACNP-BC
Clinical Team Leader
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 B
Meeting Category: Pre-NDA
Meeting Date and Time: July 1, 2013, 3:00pm EST
Meeting Location: WO22, Conference Room 1315

Application Number: IND 101254
Product Name: Idelalisib
Indication: Treatment of patients with indolent B-cell NHL (b) (4)

Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Virginia Kwitkowski, RN, MS, ACNP-BC
Meeting Recorder: Amy Baird

FDA ATTENDEES

Ann Farrell, MD, Director, Division of Hematology Products (DHP)
Edvardas Kaminskas, MD, Deputy Director, DHP
Virginia Kwitkowski, RN, MS, ACNP-BC, Clinical Team Leader, DHP
Barry Miller, Clinical Reviewer, DHP
Yun Wang, PhD, Statistical Reviewer, Division of Biometrics 5 (DB5)
Bahru Habtemariam, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 5 (DCP5)
Amy Baird, Regulatory Project Manager, DHP

Gilead Sciences, Inc.

Roy Banes, MD, PhD, Senior Vice President, Oncology and Inflammation
Roger Dansey, MD, Vice President, Clinical Research
Jason Chamberlain, PhD, MBA, Senior Research Scientist I, Drug Safety Evaluation
Xiaoming Li, PhD, Director, Biostatistics
Srin Ramanathan, PhD, Director, Clinical Pharmacology
Jennifer Stephens, Director, Regulatory Affairs
Lauren Cutler, MBS, Manager, Regulatory Affairs

(b) (4)

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.

Proposed indication: Idelalisib is indicated for the treatment of patients with indolent B-cell NHL

Indolent NHL: follicular lymphoma (FL), small lymphocytic lymphoma (SLL),

(b) (4)

Approved agents, used singly or in combination with other agents, include: chlorambucil, cyclophosphamide, rituximab, ibritumomab tiuxetan, tositumomab + ¹³¹I tositumomab, and bendamustine. Commonly used agents and regimens include: R-CHOP, R-CVP, FCMR, fludarabine, lenalidomide.

2. DISCUSSION

Question 1: Does the Agency have any comments on the proposed content for the clinical section of the NDA?

FDA Response to Question 1:

Please provide the proposed data lock date for the NDA submission. Also, whether the data from patients in study 101-07 and 101-99 will contribute to efficacy or safety conclusions will remain a review issue.

Gilead Response: Table 1 provides a summary of the data lock dates for the key efficacy and safety studies to be included in the NDA.

Table 1. Summary of Data Lock Dates

<i>Study Number</i>	<i>Data Lock Dates</i>
<i>101-09</i>	<i>12 July 2013</i>
<i>101-02^a /-99^b</i>	<i>19 June 2013</i>
<i>101-07^c /-99^b</i>	<i>19 June 2013</i>

a: Study 101-02 is complete, the data lock date was 20 December 2012

b: Study 101-99 data-cut off date was 01 May 2013

c: Study 101-07 data-cut off was 15 Feb 2013 and data lock was 29 May 2013

Could the Agency clarify if the comment regarding a review issue relates to the contribution of combination therapy?

Discussion:

Yes.

Question 2: Does the Agency have any comments on the nonclinical studies to be included in the IDELA NDA?

FDA Response to Question 2:

The pharmacology/toxicology studies presented in the Table of Contents are acceptable. We note that the embryofetal development (EFD) study was conducted in rats only. Based on the summary information of external malformations, your approach is reasonable. A final decision in regard to conducting an EFD study in a second species will be made during the NDA review.

Gilead Response: Gilead acknowledges the Agency's comment; no further discussion is necessary.

Question 3: Does the Agency agree with the proposed NDA Table of Contents?

FDA Response to Question 3:

From a technical standpoint (not content related), yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- Provide a linked reviewer's aid/ reviewer's guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application can be helpful to the reviewers.
- Meeting Minutes placed in m1.6.3 should be single pdf file (not individual files) with bookmarks, TOC and hyperlinks. Synopsis and other documents should be placed in their respective eCTD locations (not in m1).
- For archival purposes, you should also submit a pdf file of any word document and include "word" in the leaf title, so reviewers could quickly identify the word version of the document.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

- Providing one 3.2.S and 3.2.P Manufacturing section with attribute of "ALL" and differentiating documents by leaf title is acceptable. Additionally, indicating the substance/product name at the beginning of leaf title helps sorting abilities when sorting by substance or product.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF including case report forms (CRFs). Please refer to the eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM163560.pdf>
- Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml.

Gilead Response: *Gilead appreciates the Agency's additional comments and we plan to address them in the NDA. No further discussion is necessary.*

Question 4: *Does the Agency agree with the proposal for the timing and content of the IDELA NDA Safety Update?*

FDA Response to Question 4:

The 90-day safety update should also contain updated adverse reaction datasets and case report forms for each patient who died or did not complete the study due to an adverse event.

Gilead Response: *Gilead acknowledges the Agency's request and we plan to include the updated datasets and case report forms in the 90-day safety update. No further discussion is necessary.*

Question 5: *Does the Agency have any comments on the proposal for the SCE?*

FDA Response to Question 5:

No, your plan appears acceptable.

Gilead Response: *Thank you for the response. No further discussion is necessary.*

Question 6: *Does the Agency have comments on the proposal for the ISS?*

FDA Response to Question 6:

Pooled analyses should not [REDACTED] ^{(b) (4)} Please include in the pooled analysis trials 101-02, 101-09, 101-10, 101-11, and 101-99.

Gilead Response: *Gilead will present the pooled analyses of monotherapy in the ISS without combination therapy data. With reference to FDA's response to Question 1, Gilead proposes to include a separate section of pooled analyses for combination therapy.*

Question 7: *Does the Agency agree that the data standards for the Phase 1 legacy studies and Phase 2 studies are acceptable for the NDA package?*

FDA Response to Question 7:

Yes, the data standards described for the Phase 1 legacy studies and Phase 2 studies are acceptable.

Question 8: *Since DEFINE.XML files will be provided for the Phase 2 studies, can the Agency clarify the purpose of the DEFINE.PDF files to ensure that Gilead creates them appropriately to serve the intended purpose? If the Define.PDF is for printing with the Define.xml for navigation does the Agency agree that DEFINE.PDF files with no bookmarks or links are acceptable for the Phase 2 studies?*

FDA Response to Question 8:

Yes, this is acceptable.

Gilead Response: *Thank you for the response. No further discussion is necessary.*

Question 9: *Are there any other datasets the Agency would like Gilead to include in the NDA?*

FDA Response to Question 9:

No. If reviewers cannot adequately review the application with the datasets provided, the division may request additional datasets or changes to the datasets submitted after NDA submission.

Gilead Response: *Thank you for the response. Does the Agency recommend that a teleconference is scheduled to review the structure of the datasets to be provided in the NDA?*

Discussion:

A telecom is not necessary at this time.

Question 10: *Does the Agency agree that a waiver request for iNHL is appropriate?*

FDA Response to Question 10:

Yes, we agree with your plan to submit a waiver request for iNHL.

Gilead Response: *Thank you for the response. No further discussion is necessary.*

Question 11: *Does the Agency have any comments on Gilead's plans to request (b) (4) for IDELA and can they provide any clarification on the provisions associated with (b) (4)*

FDA Response to Question 11:

(b) (4)



Gilead Response: *Thank you for the response.*

Question 12: *Does the Agency have any comment on the acceptability of the data from Study 101-02, supported by data from Studies 101-07 and 101-08, supporting an accelerated approval filing with an indication for relapsed/refractory CLL?*

FDA Response to Question 12:

It is unlikely that the extent of information you have in CLL will be adequate to support an indication.

Gilead Response: *Gilead believes that the treatment effect of IDELA in CLL is highly compelling and consistent across patient populations.*

Our data demonstrate:

- *Substantial and durable monotherapy response rates in heavily pre-treated, highly refractory CLL patients*
- *Substantial and durable response rates in heavily pretreated relapsed/refractory patients with CLL in combination with rituximab, bendamustine, and rituximab plus bendamustine*
- *Substantial and durable responses in elderly untreated patients with CLL in combination with rituximab*
- *Substantial and durable responses in subpopulations of high unmet medical need (17p del) across studies and across lines of therapy with preliminary evidence that 17p del is not predictive of response to IDELA*

Furthermore, the first of 3 randomized trials of IDELA in combination with rituximab is well advanced and availability of data from this study is expected to confirm efficacy of IDELA in unselected populations with CLL.

Could the Agency comment on what “extent of information” would be adequate for inclusion in this initial NDA?

In addition, Gilead plans to submit a request for breakthrough therapy (BT) designation for the relapsed/refractory CLL indication. Provided BT designation is granted for CLL, is there an opportunity to submit CLL data to the iNHL NDA during review or to file the functional equivalent of a supplemental NDA for the CLL indication prior to approval of the original iNHL NDA?

Gilead proposes that consideration should be given to accelerated approval for IDELA for the CLL indication based on the totality and consistency of the currently available data with likely near term confirmation of the treatment effect in similar relapsed/refractory CLL populations based on randomized trial results.

Discussion:

Eleven patients with CLL received idelalisib at the proposed dose of 150mg bid in this phase 1 trial. The Division does not agree that there are enough patients with CLL at

the proposed single agent dose and schedule for an NDA submission.

It is possible to file a second indication as a second NDA while the first application is under review.

Question 13: *Does the Agency have any additional comments on Gilead’s proposed filing strategy?*

FDA Response to Question 13:

In general, single-arm trials in relapsed/refractory patient populations are appropriate for accelerated approval. In your NDA filing, be sure to fully describe your plan for verifying the clinical benefit of any indication sought for accelerated approval.

Gilead Response: *Gilead currently has 5 ongoing randomized Phase 3 studies (3 in CLL, 2 in iNHL). Gilead proposes to utilize the most mature study (GS-US-312-0116) that is likely to produce results in the near term as the confirmatory trial. Study 312-0116 is a randomized trial of rituximab ± IDELA in relapsed/refractory CLL patients with progression free survival as the primary endpoint. The study is almost completely enrolled with 175 subjects. The sample size of the study was recently increased to 200 subjects with Protocol Amendment 3 (submitted to IND 101254 on 26 June 2013, Seq 0358). In addition to the increase in sample size, 2 interim analyses were incorporated into the protocol, with the first interim analysis currently targeted for late Q3 2013.*

Based on prior precedent for regular approval supported by single-arm trials in iNHL, can the Agency please clarify if that pathway is available for IDELA.

Discussion:

This will be a review issue based on the trial results.

2.1. Additional FDA Comments

Statistical Comments

- Subgroup analyses by age, gender, race and region should be performed for the primary efficacy endpoint.

Gilead Response: *The requested subgroup analyses will be provided for Study 101-09. The age subgroups will be < 65 years and ≥ 65 years and the region subgroups will be US and Europe.*

- The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.

Gilead Response: We will provide the programs (non-executable) as requested for Studies 101-09 and 101-02/99.

- Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Gilead Response: Gilead will provide the information as requested; no further discussion is necessary.

Clinical Pharmacology Comments

For the clinical pharmacology components of your planned NDA, we recommend that you consider the following items:

- In your clinical pharmacology summary, include a comprehensive evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK, safety and efficacy of idelalisib.

Gilead Response: In the clinical pharmacology summary, the effect of covariates such as age, gender, weight, and race will be evaluated in population PK modeling of IDELA and its metabolite GS-563117 and resulting model derived exposures will be utilized for exposure-efficacy and exposure-safety analyses.

- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., DR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.

Gilead Response: Thank you for your response. Gilead will provide the information in the NDA. No further discussion is necessary.

- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of

variation, arithmetic mean \pm standard deviation, and median with range where appropriate.

Gilead Response: Gilead will provide concentration-time and derived PK parameter datasets for all studies in the NDA. The PK parameters for IDELA and its metabolite GS-563117 (where available) will be summarized in Section 15 of the Clinical Study Reports using the descriptive statistics requested by the Agency. No further discussion is necessary.

- We encourage you to refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>. For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Gilead Response: Gilead will ensure that all items are suitably addressed in the Population PK report. No further discussion is necessary.

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/s/

VIRGINIA E KWITKOWSKI
08/07/2013

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[®] (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[®] (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

Patrick Zhou, 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[®] (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.



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, (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.

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/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

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/s/

ANN T FARRELL
05/22/2014