CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205858Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	205858
Applicant Name	Gilead Sciences, Inc.
Date of Submission	September 11, 2013
PDUFA Goal Date	September 11, 2014
Proprietary Name / **Established (USAN) Name**	Zydelig/idelalisib
Dosage Forms / Strength	150 mg and 100 mg tablets
Proposed Indication(s)	NDA 205858: indicated for the treatment of patients with refractory indolent non-Hodgkin lymphoma
Action/Recommended Action for NME:	**Accelerated Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Barry Miller, MSN, CRNP, Donna Przepiorka, M.D., Ph.D., /Angelo DeClaro, M.D.,
Statistical Review	Kyung Lee, Ph.D., /Lei Nie, Ph.D./ Raji Sridhara, Ph.D.
Pharmacology Toxicology Review	Natalie Simpson, Ph.D., Ramdevi Gudi, Ph.D./Haleh Saber, Ph.D./John Leighton, Ph.D.
CMC Review/OBP Review	Debasis Ghosh, Ph.D.,Li Shan Hsieh, Ph.D./Ali Al-Hakim, Ph.D.,/Sandra Suarez Sharp, Ph.D./Angelica Dorantes, Ph.D./Ramesh Sood, Ph.D.
Microbiology	Jessica G. Cole, Ph.D./Bryan Riley, Ph.D.
Clinical Pharmacology Review	Stacy Shord, Pharm.D./Julie Bullock, Pharm.D., Dhananjay D. Marathe, Ph.D./Nitin Mehrotra, Ph.D./Rosane Charlab Orbach, Ph.D.
OSI	Anthony Orencia, M.D./Janice Pohlman, M.D., M.P.H., Kassa Ayalew, M.D., M.P.H.
CDTL Review	Angelo DeClaro, M.D.
OSE	Kathleen Davis/Karen Rulli/Kate Henirich Oswell/Kevin Wright/Carole Braodnax/Naomi Redd, Pharm.D., Cynthia LaCivita, Pharm.D./ Claudia Manzo, Pharm.D./ Yelena Maslov, Pharm. D.
QT-IRT	Moh Jee NG, Qianyu Dang, Hongshan Li, Kevin M Krudys, Monica L Fiszman, Norman L Stockbridge

Signatory Authority Review Template

1. Introduction

Gilead has submitted two NDAs for its NME Zydelig, idelalisib. NDA 205858 was submitted on September 11, 2013 for the following indication: for the treatment of patients with refractory indolent Non-Hodgkins Lymphoma. NDA 206545 was submitted on December 6, 2013 for the treatment of relapsed chronic lymphocytic leukemia. NDA 205858 was given standard review. NDA 206545 was given a priority review. Idelalisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor. No PI3K kinase inhibitors are approved at this time for treatment of hematologic malignancies. The pharmacologic class is kinase inhibitor.

Zydelig is not approved in any country at this time.

2. Background

Non-Hodgkin's Lymphoma (NHL) is a heterogeneous group of lymphomas with a variable prognosis. NHL subcategories include aggressive, indolent, etc. This application concerns the indolent NHL subcategory. The applicant enrolled patients with the following histologic subtypes in the major trial for consideration: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, and marginal zone lymphoma. Due to too few patients enrolled with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia and marginal zone lymphoma, the review team focused their efforts on the patients enrolled with FL and SLL.

From Mr. Barry Miller's and Dr. Prezpiorka's review:
Approximately 20,500 patients will be newly diagnosed with FL or SLL in the US this year. Three-year progression free survival is estimated to range from 51 to 91% with a 3 year survival rate of 84 to 91%...

No curative treatments exist for relapsed FL and SLL. The standard of care for patients with symptoms is to administer cytoreductive chemotherapy repeatedly until fatal resistant disease occurs…

Although there are several active combinations of cytotoxic chemotherapeutics or

radioimmunotherapeutics that can be used for treatment of relapsed FL or SLL, efficacy is variable, and the durations of response are limited. Moreover, repeat administration of intravenous combination chemotherapy with its attendant myelosuppression poses additional challenge.

3. CMC/Device

No issues were identified that would preclude approval.

From the review:

Zydelig tablets, 100 mg and 150 mg, are packaged in 60 mL, white, high density polyethylene (HDPE) bottles with a polyester fiber coil. Each bottle contains sixty (60) tablets and is capped using a white, continuous thread, child-resistant (b) (4) *screw cap with an* (b) (4) *aluminum foil liner.*

The product shelf life recommendations are for 24 months stored below 30^0 C. Any extension of the expiry period will be based on submission of additional data.

Post-approval commitments are recommended as described in Section 13 of this review.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the secondary review:

Idelalisib-related toxicities in rats and dogs included findings in the following organs: liver (increased ALT, AST, and GGT, inflammation, and necrosis), heart (cardiomyopathy, inflammation, and fibrosis), pancreas (inflammation and low incidence acinar degeneration), lung (infiltration, alveolar macrophages), lymphoid tissues (depletion of lymphocytes), GI tract including the tongue (ulceration, hemorrhage, and inflammation), and male reproductive organs (spermatid depletion, testicular seminiferous tubule degeneration). Hemorrhage was occasionally observed, those included hemorrhage in the GI tract, thymus, and brain. Several of the toxicities reported (e.g. inflammation, cardiomyopathy, pancreatic acinar degeneration) may be due to the inhibition of CXCR4/5 pathways. Of note, CXCR5 is upstream from Bruton's tyrosine kinase (BTK). Inhibition of the BTK pathway may be associated with multiorgan inflammation and pancreatic acinar cell degeneration.

In pigmented Long-Evans rats, skin and eye uvea showed higher concentrations of idelalisib than that observed in Sprague-Dawley rats, suggesting that idelalisib or idelalisib-related materials (e.g. metabolites) bind to melanin. Clinical signs of, skin

erythema and swelling have been reported in animals in the toxicology studies with low incidence of mononuclear infiltration.

Idelalisib was not genotoxic in the bacterial mutagenesis (Ames) assay or in vitro chromosome aberration assay using human peripheral blood lymphocytes. Idelalisib was genotoxic in male rats in the in vivo micronucleus study; however, only at a high dose of 2000 mg/kg.

Two separate fertility studies were conducted. In one of the studies, male rats treated with idelalisib were mated with untreated females. Idelalisib caused decreased weight in epididymis and testis; however, there were no adverse effects on fertility parameters. In the second study, female rats given idelalisib were mated with untreated males. There were no adverse effects on fertility parameters in this study; however, there was a decrease in the number of live embryos at the highest dose tested. In an embryo-fetal developmental study, idelalisib caused malformations in rats when given to pregnant animals during the period of organogenesis at maternally toxic doses. Therefore, pregnancy category D is recommended…

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified.

The review stated:

> *The proposed dose of 150 mg BID is reasonable and noted that dropping the dose might result in less activity*
> *No dose adjustment is needed for patients taking acid-reducing agents*
> *No dose adjustment is needed for patients with hepatic impairment*
> *No dose adjustment is needed for patients taking a strong CYP3A inhibitor or inducer*

From the OT-IRT review:
No significant QTc prolongation effects of idelalisib (150 mg and 400 mg) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib (150 mg and 400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcN for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

From the primary clinical review for the indolent lymphoma indication (NDA 205858):

This review team recommends approval of idelalisib under Subpart H (21 CFR 314.510) for treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) after two or more prior systemic therapies, and for treatment of patients with relapsed small lymphocytic lymphoma (SLL) after two or more prior systemic therapies. Accelerated approval is based on the finding of durable complete or partial responses. Confirmation of clinical benefit is required.

Approval for these indications is supported by the results of Protocol 101-09, a single-arm trial of idelalisib 150 mg BID in patients with indolent lymphomas. The applicant proposed that idelalisib (b) (4)

It remains to be confirmed in post-marketing studies that idelalisib is efficacious, safe, and tolerable in patients with FL and SLL when taken for an extended duration, i.e., 12 months or longer. The optimal idelalisib dosing regimen for chronic administration is unknown…

The efficacy of Zydelig was evaluated in 123 patients with previously treated indolent non-Hodgkin lymphomas in the single arm Phase 2 Trial 101-09. All patients were started on continuous oral dosing of 150mg twice daily. The primary endpoint was overall response rate (ORR) as determined by an independent review committee (IRC). A key secondary endpoint was duration of response (DOR).

For all patients on trial, the ORR was 55% (95% CI: 46, 64) with a median DOR of 12.5 months. By lymphoma type, a summary of key efficacy results follow:
• In patients with follicular lymphoma, the ORR was 54% (39 of 72 patients). The median DOR was not evaluable. Median follow-up was 8.1 months.
• In patients with small lymphocytic lymphoma, the ORR was 58% (15 of 26 patients) with a median DOR of 11.9 months.

There were inadequate numbers of patients with marginal zone lymphoma (15 patients) and lymphoplasmacytic lymphoma (10 patients) (b) (4)

For the FL and SLL populations, limitations of the efficacy data include a relatively short exposure to idelalisib and a short duration of response.
• Only 33 patients (24 FL, 9 SLL) remained on idelalisib longer than six months
• Only 10 patients (5 FL, 5 SLL) were treated for more than 12 months.
• 9 patients (6 FL, 3 SLL) had duration of response of less than two months which represented 17% of the patients with responses.
• 89% of patients with response had a DOR shorter than 12 months.
• 54% of patients with responses had a DOR shorter than 6 months.

I concur with the findings of the clinical and statistical review teams.

8. Safety

The major safety issues identified with use of this product in clinical trials include: hepatoxicity (including fatalities), diarrhea/colitis with perforation, pneumonitis, infection, rash, neutropenia, fatigue, cough, nausea, pyrexia, and abdominal pain. The first three adverse reactions listed above are in a boxed warning in the labeling. Due to the seriousness of the adverse reactions and fatalities, A REMS program (communication) will be used to ensure that prescribers are aware of the risks associated with use.

9. Advisory Committee Meeting

No clinical efficacy or safety issues arose that required an Advisory Committee meeting.

10. Pediatrics

This product has orphan designation for these indications.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) report stated the following:
The study data collected from these clinical sites that have been inspected and submitted by the sponsor appear generally reliable in support of the requested indication.

Financial Disclosure information was provided and reviewed. None of the investigators had disclosable financial interests or arrangements.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval with post-marketing commitments to confirm clinical benefit

- Risk Benefit Assessment

Relapsed follicular lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) are serious and life-threatening illnesses without a curative therapy except for an allogeneic stem cell transplant. The typical clinical course for those who do not undergo a transplant is characterized by multiple relapses. This product does produce partial responses in patients with indolent NHL (FL and SLL) whose disease has progressed after use of other therapies. However these partial responses are not suggestive of a cure nor clinical benefit, and only limited information exists on tolerability of the product based on the short duration of treatment is in the trial. The major safety issues identified with use of this product in clinical trials include: hepatoxicity (including fatalities), diarrhea/colitis with perforation, pneumonitis, infection, rash, neutropenia, fatigue, cough, nausea, pyrexia, and abdominal pain. The first three adverse reactions listed above are in a boxed warning in the labeling. Due to the seriousness of the adverse reactions and fatalities, A REMS program (communication) will be used to ensure that prescribers are aware of the risks associated with use.

In addition to the safety labeling, there will be additional PMR/PMCs to provide information on clinical benefit and safe product use.

- Recommendation for Post marketing Risk Management Activities
  This product will have a REMS consisting of a communication plan to ensure understanding of the serious risks associated with this product. The risks include hepatoxicity including fatalities, bowl perforation, colitis and pneumonitis.

- Recommendation for other Post marketing Study Requirements/ Commitments

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

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

PMR 2180-3 Submit the complete study report and data showing clinical efficacy and safety from trial 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 2180-4 Conduct a study to characterize the incidence, diagnosis and effective treatment of Zydelig-related pneumonitis based on data and pooled analyses from randomized trials in iNHL and CLL (0115, 0119, 0124, and 0125).

PMR 2180-5 Conduct a trial to 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 trial 101-99 Phase 1/2 extension study of safety and durability of idelalisib in hematologic malignancies.

PMR 2180-6 Conduct a trial to 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 trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.

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

Refer to action letter for final wording and milestones of the post-marketing requirements.

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

/s/

ANN T FARRELL
07/15/2014