CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206545Orig1s000

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 #**	206545
Applicant Name	Gilead Sciences, Inc.
Date of Submission	December 6, 2013
PDUFA Goal Date	August 6, 2014
Proprietary Name / **Established (USAN) Name**	Zydelig/idelalisib
Dosage Forms / Strength	150 mg and 100 mg tablets
Proposed Indication(s)	NDA 206545: indicated for the treatment of relapsed chronic lymphocytic leukemia
Action/Recommended Action for NME:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Nicole Gormley, M.D./Angelo DeClaro, M.D.,
Statistical Review	Sirisha Mushti, Ph.D./Yuan Li Shen, 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 first phosphatidylinositol 3-kinase (PI3K) inhibitor. No PI3K kinase inhibitors are approved at this time for treatment of hematologic malignancies. The pharmacologic class is a kinase inhibitor.

Zydelig is not approved in any country at this time.

2. Background

From Dr. Gormley's review:
Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative neoplasm characterized by the clonal proliferation and accumulation of mature B lymphocytes. It is the most common leukemia in the United States, accounting for 30% of all leukemias. It is estimated that there will be 15,680 new cases of CLL, and 4,580 deaths from CLL in the year 2013(Siegel et al.). There is a slight male predominance (1.7:1), and the disease occurs more frequently in the elderly, with a median age at diagnosis between 67- 72 years. Two thirds of cases are diagnosed among those aged ≥ 65 (Danilov, 2013).

CLL is a heterogeneous disease with variable clinical course and outcome. Treatment is not indicated in all patients with CLL; as there is no benefit for treating early stage asymptomatic CLL(Desablens et al., 2013). Treatment is typically reserved for those that are symptomatic, or have progressive or high risk disease. CLL patients are categorized into risk groups based on the clinical staging systems, Rai and Binet. Other prognostic factors which help guide treatment include: lymphocyte doubling

time, cytogenetic abnormalities, biological prognostic factors (IGHV), serum markers, and mutational status. A hierarchical model of risk in CLL based on common genetic abnormalities was developed by Döhner(Döhner et al., 2000). This study demonstrated that individuals with deletion 17p and 11q have significantly shorter survival times and poorer response to treatment…

CLL is not a curable disease, except in the setting of hematopoietic stem cell transplant. For physically fit patients, chemoimmunotherapy regimens (eg. fludarabine, cyclophosphamide, and rituxumab (FCR); bendamustine and rituximab (BR); or pentostatin, cyclophosphamide, and rituximab (PCR)) are the standard of care. For patients that are physically unfit with significant comorbidity, treatment with chlorambucil with or without rituximab or rituximab alone is the current standard of care (Zelenetz et al., 2013). At the time of relapse, treatment with the initial regimen can be pursued if the treatment-free interval is longer than 2 years. If relapse occurs earlier, alternative therapies should be used. Patients with del(17p) or TP53 mutation that achieve a CR or PR to first-line therapy, that are physically fit, should be considered for stem cell transplant…

I concur with her understanding and conclusions regarding available therapy.

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 that:

> *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 Chronic Lymphocytic Leukemia indication (NDA 206545):

I recommend regular approval for Idelalisib in combination with rituximab for the treatment of adult patients with relapsed CLL, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities…The basis for regular approval is based on a single, randomized, placebo-controlled trial, Study 312-0116, which demonstrated an improvement in progression-free survival among patients with relapsed CLL that had comorbidities…

Clinical benefit. *The efficacy of Idelalisib was evaluated in study 312-0116, in which 220 patients were randomized to receive either Idelalisib 150 mg orally BID in combination with 8 doses of rituximab (first dose at 375 mg/m2, subsequent doses at 500 mg/m2 every 2 weeks for four infusions and every 4 weeks for an additional 4 infusion) or placebo in combination with rituximab. Subjects continued treatment with Idelalisib or placebo until disease progression, unacceptable toxicity, or the end of study. A Type A meeting was held between the Agency and the applicant on October 7, 2013 to discuss early termination of Study GS-US-312-0116 for efficacy based on the results of an interim analysis. The clinical trial was terminated early on October 9, 2013.*
A summary of the key efficacy findings are listed below. The data cutoff date for the efficacy analysis was October 9, 2013.
• The primary endpoint was PFS as assessed by the IRC. PFS between the two treatment arms was compared using a stratified log-rank test, adjusted for the stratification factors: 17p deletion and/or TP53 mutation status and IGHV mutation status. The IRC assessed PFS hazard ratio of the ITT population was

0.18 (95% CI: 0.10, 0.31) stratified log-rank p value <0.0001.
• The median PFS was not reached in the Idelalisib + rituximab group at the time of the interim analysis, and was 5.5 months in the placebo + rituximab group.
• Overall response rate was a secondary endpoint. There were no complete responses (CRs) in either treatment arm. There were 82 partial responses (PR) in the Idelalisib + rituximab arm (overall response rate-74.5%), and 16 partial responses in the placebo + rituximab arm (overall response rate- 14.5%).
• Overall survival was a secondary endpoint. The analysis of overall survival is limited by the small number of events (19 events).

Risk. *The safety population for Study 312-0116 consisted of 218 subjects who received at least one dose of study drug. The key safety findings are listed below:*
• The Idelalisib dose was 150 mg orally BID. The median exposure duration to Idelalisib was 5.0 months (range: 0.3, 17.3).
• Thirty- nine (39) subjects (35.5%) in the Idelalisib arm and 19 subjects (17.6%) in the placebo arm had a dose interruption due to adverse reactions or lab abnormalities. Sixteen (16) subjects in the Idelalisib arm (14.5%) had a dose reduction due to adverse reactions or lab abnormalities. No subjects in the placebo arm required a dose reduction. Twelve (12) subjects in the Idelalisib arm discontinued study drug due to an adverse event, and 12 subjects in the placebo arm discontinued due to an adverse event.
• Serious adverse reactions were reported in 54 (49.1%) subjects treated with Idelalisib+ rituximab compared to 38 patients (35.2%) in the placebo arm. The most frequent serious adverse reactions that were observed more frequently in the Idelalisib arm were pneumonia (13.6%), pyrexia (9.1%), sepsis (7.3%), pneumonitis (3.6%), and diarrhea (2.7%).
• Additional safety issues have been identified with the use of Idelalisib; including bowel perforation, colitis, AST/ALT elevations, serious and fatal hepatotoxicity, and severe cutaneous skin reactions.

Benefit-Risk Assessment*. In Study 312-0116, Idelalisib in combination with rituximab demonstrated a significant improvement in PFS compared to rituximab alone (+ placebo). Single-agent rituximab in patients with relapsed disease has limited clinical activity. It is difficult to confidently characterize the benefits of Idelalisib given the limitations of the control arm. Single-agent rituximab is generally restricted to those individuals that have serious comorbidities that would not tolerate standard immunochemotherapy. In study 312-0116, eligibility was based on CIRS scoring, which has not been validated in hematologic malignancies. It is not clear whether the trial adequately identified patients who could not tolerate standard immunochemotherapy. Given the safety findings noted in this potentially more fit patient population, the safety in a truly frail patient population is questionable. Additionally, it is difficult to assess the proposed indication of use of Idelalisib until disease progression or unacceptable toxicity. Since there were no complete responses observed, only partial responses, it is expected that patients will remain on Idelalisib for extended durations. The median duration of Idelalisib exposure was only 5 months in Study 312-0116. Therefore, the safety of long-term administration of*

Idelalisib cannot be assessed. Idelalisib has demonstrated activity in relapsed CLL. However, the projected benefits outweigh the projected risks only if there are additional risk management strategies in place to ensure the safe use in the intended patient population.

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 this indication.

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

Regular Approval

- Risk Benefit Assessment

This product does produce responses and demonstrated a statistically significant improvement in progression-free survival (PFS) over rituximab alone for patients with CLL whose disease has relapsed. The trial was stopped for efficact following the first pre-specified interim analysis. The major labeling issue that arose during internal deliberations was how to identify a population who were unable to tolerate standard chemoimmunotherapy due to co-existing medical conditions which would be able to tolerate combination of Zydelig and rituximab. 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.

- 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

Please see approval letter for NDA 205858 for PMR/PMC related to the iNHL indication.

PMR 2180-9 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with an anti-CD20 regimen. Submit the complete study report and data from trial GS-US-312-0119, a Phase 3, randomized, study of idelalisib in combination with ofatumumab in patients with previously treated CLL.

PMR 2180-10 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in a combination therapy regimen. Submit the complete study report and data showing long-term safety with 5 years of follow-up from trial GS-US-312-0117, a Phase 3, 2 arm, extension study of idelalisib in patients with previously treated CLL.

Refer to action letter for NDA 206545 for final wording and milestones of the postmarketing
requirements. Refer also to action letter for NDA 205858 for other
PMRs.

- Recommended Comments to Applicant

None

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/s/

ANN T FARRELL
07/15/2014