CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 206545
Applicant	Gilead Sciences, Inc.
Date of Submission	6 December 2013
PDUFA Goal Date	6 August 2014
Proprietary Name / Established (USAN) names	Zydelig (idelalisib)
Dosage forms / Strength	Tablets, 100 mg and 150 mg
Proposed Indication(s)	Treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
Recommended:	*Approval*

Material Reviewed/Consulted	Reviewer
Division Director	Ann Farrell, MD
RPM	Mara Miller
Clinical Review	Nicole Gormley, MD / Angelo DeClaro, MD
Statistical Review	Sirisha Mushti, PhD / Yuan-Li Shen, PhD
Pharmacology Toxicology Review	Natalie Simpson, PhD, Ramadevi Gudi, PhD / Haleh Saber, PhD / John Leighton, PhD
ONDQA-CMC and Biopharmaceutics Reviews	CMC: Debasis Ghosh, PhD, MPharm (Drug substance)/ Li Shan Hsieh, PhD (Drug product)/Ali Al-Hakim, PhD Biopharm: Sandra Suarez Sharp, PhD /Angelica Dorantes, PhD Microbiology: Jessica Cole, PhD / Bryan Riley, PhD ONDQA: Ramesh Sood, PhD (Tertiary Review)
Clinical Pharmacology Review	DCP V: Stacy Shord, PharmD, Julie Bullock, PharmD Pharmacogenomics: Rosane Charlab Orbach, PhD Pharmacometrics: Dhananjay Marathe, PhD, Nitin Mehrotra, PhD
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1. Introduction

On December 6, 2013, Gilead Sciences, Inc. submitted an NDA for Zydelig (idelalisib) for the proposed indication of treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Zydelig (idelalisib) is a new molecular entity inhibitor of PI3Kδ, the delta isoform of phosphatidylinositol 3-kinase. PI3Kδ is a downstream signal transducer for several receptors including B-cell receptor (BCR), CD40 receptor, chemokine receptor CXCR5, IL-6 receptor, and integrins. These pathways may be involved in B-cell proliferation, motility, and in homing to and maintenance of the tumor microenvironment in B-cell malignancies. There are no approved PI3K inhibitors.

The primary basis for the application are the results of clinical trial 312-0116, a randomized, double-blind, placebo-controlled trial of idelalisib in combination with rituximab in patients with relapsed CLL, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Supportive clinical trials include single-arm trials of idelalisib combined with rituximab or chemo-immunotherapy regimens, and monotherapy idelalisib trials referenced in NDA 205858.

2. Background

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 2013. 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 and 72 years.

CLL is a heterogeneous disease with variable clinical course and outcome. Treatment may not be indicated in all patients with CLL; as benefit has not been established for treating early stage asymptomatic CLL. Treatment is typically reserved for those who are symptomatic, or have progressive disease.

CLL is not a curable disease, except in the rare setting of an allogeneic hematopoietic stem cell transplant. For physically fit patients, chemo-immunotherapy regimens (e.g., fludarabine, cyclophosphamide, and rituxumab (FCR); bendamustine and rituximab (BR); or pentostatin, cyclophosphamide, and rituximab (PCR)) are commonly used. For patients that are physically unfit with significant comorbidity, treatment with chlorambucil with or without rituximab or rituximab alone is used. 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 are used. Patients with del(17p) or TP53 mutation that achieve a CR or PR to first-line therapy, that are physically fit, are considered for stem cell transplantation. FDA-approved drugs for the treatment of CLL are following: chlorambucil, cyclophosphamide, fludarabine, alemtuzumab, bendamustine, ofatumumab, rituximab, obinutuzumab and ibrutinib.

3. CMC/Device

The Chemistry review team recommends an overall acceptability regarding the manufacturing of the drug product and drug substance. Zydelig (idelalisib) tablets are an immediate release product to be marketed as 100 mg and 150 mg strengths. An expiration period of 24 months is granted for the product. The drug product is stored at 25°C with excursions permitted 15-30ºC (59-86ºF). Also, the Office of Compliance issued an overall acceptable recommendation for this application.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical findings that would preclude the approval of idelalisib for the proposed indication.

In *in vivo* and *in vitro* safety pharmacology studies conducted, no clear drug-related effects were observed for idelalisib on neurological, cardiovascular, or respiratory function. However, drug-related cardiomyopathy and an increase in heart weight were observed in the rat in the repeat-dose toxicology studies.

Toxicities following repeated dosing of idelalisib in rats and/or dogs included findings in the following tissues/organs:

- hematopoietic/lymphoid system (lymphoid depletion, reduced weight of spleen and thymus, thymic hemorrhage and necrosis, myeloid and granulopoeitic hyperplasia),
- liver (increased liver enzymes, increased liver weight, inflammation, hepatocellular necrosis),
- gastrointestinal tract including the tongue (infiltration, hemorrhage, ulceration),
- heart, seen in rats only (myocardium infiltrate, fibrosis, increased heart weight);
- male reproductive systems (testicular seminiferous tubule degeneration, reduced testicular weight).

Inflammation was observed in several tissues (e.g. in the GI tract, pancreas, lungs, heart, and liver) and may be related to the inhibition of the CXCR5 pathway, involved in homing of B-cells. Skin may be also a target of idelalisib toxicity. In pigmented rats, idelalisib-related radioactivity was present in the eyes and skin at higher concentrations than what were reported for non-pigmented rats. Skin erythema, dryness, swelling, and redness have been observed in animals in toxicology studies.

General toxicology studies were done and included 28-day studies in rats and dogs, a 13-week study in rats, a 6-month study in rats, and a 9-month study in dogs. There were mortalities in all rat studies with cause of deaths undetermined or related to liver toxicity. Cardiomyopathy was observed in unscheduled sacrifices and surviving rats in the 13-week and 6-month studies,

with an increase in heart weight observed in the 13-week study. In the 9-month dog study, mortality was attributed to systemic inflammation, with no signs of hepatotoxicity in this study.

Carcinogenicity: Idelalisib did not induce mutations in the bacterial mutagenesis (Ames) assay and, was not clastogenic in the *in vitro* chromosome aberration assay using human peripheral blood lymphocytes. Idelalisib was genotoxic in males in the *in vivo* rat micronucleus study at a high dose of 2000 mg/kg. Carcinogenicity studies with idelalisib have not been conducted.

Reproductive toxicology: 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

There are no clinical pharmacology findings that would preclude the approval of idelalisib.

Absorption and Food Effect. Idelalisib exposure increased in a less than dose proportional manner with doses up to 350 mg in fasted conditions; it demonstrates dose-dependent absorption. The median T_{max} was observed at 1.5 h (range 0.5, 6 h) under fasted conditions. The administration of a single 400 mg dose of idelalisib with a high-fat meal resulted in a 1.4-fold increase in AUC. Idelalisib should be administered without regard to food. In the NHL and CLL trials, idelalisib was administered without regard to food.

Metabolism and Half-Life. Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and CYP3A. GS-563117 is inactive against PI3Kδ *in vitro*. Idelalisib undergoes minor metabolism by UGT1A4. The population apparent systemic clearance at steady-state is 14.9 L/hr. The population terminal elimination half-life of idelalisib is 8.2 hours.

Drug-drug interactions: Rifampin decreased idelalisib AUC by 75%. Idelalisib should not be coadministered with strong CYP3A inducers. Ketoconazole increased idelalisib AUC by 1.8-fold. No dose adjustment is recommended for patients taking strong CYP3A inhibitors with idelalisib.

Idelalisib or its metabolite inhibited CYP3A, CYP2C19, P-glycoprotein (P-gp), OATP1B1 and OATP1B3 *in vitro*. Idelalisib increased midazolam AUC by 5.4-fold; therefore, idelalisib should not be coadministered with sensitive CYP3A substrates. No changes in exposure to rosuvastatin (OAT1B1 and OATP1B3) or digoxin (P-gp) were observed.

More diarrhea and rash were observed in patients taking idelalisib with proton pump inhibitors (PPI) (CYP2C19). Overlapping toxicities or a CYP-mediated drug interaction could be responsible for the additional adverse events.

Pathway of elimination: Approximately 78% and 14% of the radioactivity was excreted in feces and urine, respectively following a single 150 mg oral dose of [^{14}C]-labeled idelalisib. GS-563117 accounted for most of the radioactivity in plasma (62%), urine (49%) and feces (44%).

Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment. Body weight and hepatic impairment influence exposure to idelalisib. Body weight was maintained in the final population PK model, but body weight has no clinically meaningful effect on exposure. Hence, no dose adjustment is needed for body weight.

No dose adjustment is needed for patients with creatinine clearance (CLcr) ≥ 15 mL/min, since the exposure was only increased 1.3-fold in patients with CLcr 15 to 29 mL/min.

No dose modifications are recommended in patients with baseline hepatic impairment. The AUC increased up to 1.7-fold in subjects with ALT or AST or bilirubin greater than the ULN compared to healthy subjects. However, no exposure-response relationship was observed for selected safety endpoints with the exception of diarrhea in the NHL population.

The remaining covariates assessed in the population PK model had no impact on exposure, including age, race, gender, background therapies, baseline serum creatinine, and CLcr.

QT assessment
tQT Study. The effect of Zydelig (150 mg and 400 mg) on the QT/QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in 46 healthy subjects. At a dose 2.7 times the maximum recommended dose, Zydelig did not prolong the QT/QTc interval (i.e., not greater than 10 ms).

6. Clinical - Efficacy

The efficacy of Zydelig was evaluated in clinical trial 312-0116, in which 220 patients were randomized to receive either idelalisib 150 mg orally BID in combination with 8 doses of rituximab or placebo in combination with rituximab. Subjects continued treatment with idelalisib or placebo until disease progression, unacceptable toxicity, or the end of study. The clinical trial was designed with progression free survival (PFS) as the primary endpoint and the secondary endpoints in the following order: objective response rate (ORR), lymph node response rate, and overall survival (OS).

The median age was 71 (range 47, 92) with 78% over 65; 66% were male, 90% were Caucasian. The median time since diagnosis was 8.5 years. The median number of prior therapies was 3. Nearly all (96%) subjects had received prior anti-CD20 monoclonal antibodies. The most common (>15%) prior regimens were: bendamustine + rituximab (98 subjects, 45%), fludarabine + cyclophosphamide + rituximab (75 subjects, 34%), single-agent rituximab (67 subjects, 31%), fludarabine + rituximab (37 subjects, 17%), and chlorambucil (36 subjects, 16%).

A Type A meeting was held between the Agency and the Applicant on October 7, 2013 to discuss early termination of clinical trial GS-US-312-0116 for efficacy based on the results of the planned first interim analysis (65 PFS events) with a data cutoff of August 30, 2013. The data cutoff date for the efficacy analysis was October 9, 2013 and included a total of 75 PFS events. Breakthrough Therapy designation was granted on November 8, 2013 for Zydelig for the treatment of patients with relapsed CLL.

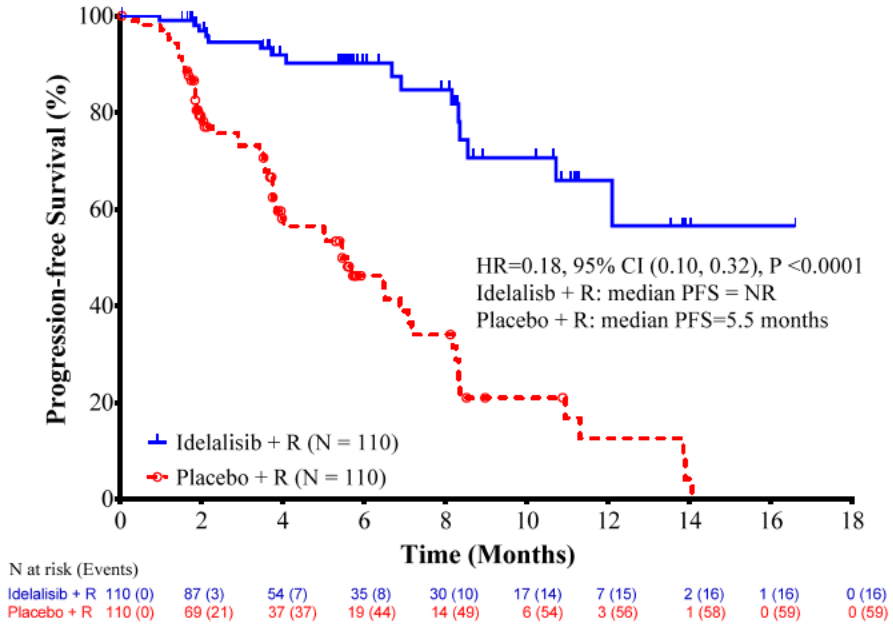
The trial was stopped for efficacy following the first pre-specified interim analysis. Results of a second interim analysis continued to show a statistically significant improvement for Zydelig + rituximab over placebo + rituximab for the primary endpoint of PFS (HR: 0.18, 95% CI (0.10, 0.32), p < 0.0001). The efficacy results are shown in Table 1 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 1: Efficacy Results from Clinical Trial 312-0116

		Zydelig + Rituxumab N=110	Placebo + Rituximab N=110
PFS	Median (months) (95% CI)	NR (10.7, NR)	5.5 (3.8, 7.1)
	Hazard ratio (95% CI)	0.18 (0.10, 0.32)	
	P-value	< 0.0001 †	

NR: not reached; † The p-values for PFS was based on stratified log-rank test.

Figure 1: Kaplan-Meier Plot of IRC-Assessed PFS



ORR 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 (ORR=74.5%), and 16 partial responses in the placebo + rituximab arm (ORR= 14.5%).

OS was a secondary endpoint. The analysis of OS was limited by the small number of events (19 deaths). In addition, the significance level for interim analysis of OS was not specified in the protocol. The protocol and statistical analysis plan lacked detail whether the trial was powered for OS.

7. 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.

8. Advisory Committee Meeting

The application for Zydelig was not referred to an FDA advisory committee because the application did not raise significant public health questions.

9. Pediatrics

Idelalisib was granted Orphan Drug Designation for this indication and is exempt from pediatric study requirements. Zydelig has not been evaluated in pediatric patients.

10. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Regular Approval

- Risk Benefit Assessment
  The efficacy and safety results from clinical trial 312-0116 demonstrate an acceptable benefit-risk profile for the treatment of patients with relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

  Zydelig's safety and effectiveness to treat relapsed CLL were established in a clinical trial of 220 participants who were randomly assigned to receive Zydelig and rituxumab or placebo and rituximab. The trial was stopped for efficacy following the first pre-specified interim analysis point, which showed an improvement in PFS with Zydelig (10.7 months in the Zydelig and rituxumab arm compared to 5.5 months for the placebo and rituxumab arm). Results from a second interim analysis continued to show a statistically significant improvement for Zydelig and rituxumab over placebo and rituxumab.

  The safety profile for Zydelig (as monotherapy or in combination with rituximab) is notable for substantial toxicities, including fatalities. The labeling will include boxed warnings for the following fatal and serious toxicities: hepatotoxicity, diarrhea and colitis, pneumonitis, and intestinal perforation. Additional items in Warnings and Precautions include severe cutaneous reactions, neutropenia, and embryo-fetal toxicity. A Medication Guide will be required.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  A REMS communication plan is required to address the risks of hepatotoxicity, intestinal perforation, colitis, and pneumonitis.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter.

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/s/

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07/21/2014

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07/22/2014