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 205858
Applicant	Gilead Sciences, Inc.
Date of Submission	September 11, 2013
PDUFA Goal Date	September 11, 2014
Proprietary Name / Established (USAN) names	Zydelig (idelalisib)
Dosage forms / Strength	Tablets, 100 mg and 150 mg
Proposed Indication(s)	1. Treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies 2. Treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies
Recommended:	Accelerated Approval

Material Reviewed/Consulted	Reviewer
Division Director	Ann Farrell, MD
RPM	Mara Miller
Clinical Review	Barry Miller, MS, CRNP / Donna Przepiorka, MD, PhD/Angelo DeClaro, MD
Statistical Review	Kyung Lee, PhD / Lei Nie, 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
OSI/DGCPC	Anthony Orencia, MD / Janice Pohlman, MD, MPH
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Patient Labeling Team (DMPP)	Nathan Caulk, MS, BSN, RN / Barbara Fuller RN, MSN, CWOCN

1. Introduction

On September 11, 2013, Gilead Sciences, Inc. submitted an NDA for Zydelig (idelalisib) for the proposed indication of the treatment of patients with refractory indolent non-Hodgkin lymphoma.

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 from clinical trial 101-09, an open-label, multi-center, Phase 2 trial of idelalisib monotherapy in patients with relapsed follicular lymphoma (FL), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), or lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia (LPL ± WM). Supportive clinical trials include idelalisib monotherapy trials in patients with lymphoid malignancies, and idelalisib single-dose and multi-dose trials in healthy volunteers.

2. Background

The National Cancer Institute estimates that 70,800 newly diagnosed cases of non-Hodgkin lymphoma (NHL) and 18,990 deaths will occur in 2014. The clinical presentation of NHL varies and depends upon the type of lymphoma and areas of involvement. Some NHLs behave indolently with lymphadenopathy waxing and waning over years.

Based on the Non-Hodgkin Lymphoma Classification Project, follicular lymphoma is the most common indolent subtype of NHL accounting for 22% of cases of non-Hodgkin lymphomas. Extranodal marginal zone accounted for 8% of NHL, SLL for 7%, nodal marginal zone for 2%, LPL for 1%, and splenic marginal zone for <1%.

The clinical course for low-grade NHL is characterized by multiple relapses. There are five currently available agents approved for the treatment of patients with follicular lymphoma, low-grade NHL, or indolent NHL: chlorambucil, cyclophosphamide, rituximab, ^{90}Y-ibritumomab tiuxetan, and bendamustine. None of the approved therapies are curative for relapsed FL or relapsed SLL.

3. CMC

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 123 patients with previously treated indolent NHL 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).

The median time from initial diagnosis to treatment on trial was 5.2 years and ranged from 0.4 to 18.4 years. The median number of prior regimens was 4. As mandated for trial inclusion, all patients received at least 2 regimens and all received rituximab and an alkylating agent as part of their prior regimens. The most common prior combination regimens were BR[1] (47%), R-CHOP[2] (46%), and R-CVP[3] (28%). Of the patients with follicular lymphoma, 51% received R-CHOP, 49% BR, and 28% R-CVP. Of the patients with small lymphocytic lymphoma, 69% received BR, 46% FCR[4], and 35% R-CHOP.

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 SLL, 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) [redacted] (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.

[1] Bendamustine, Rituximab
[2] Rituximab, Cyclophosphamide, doxorubicin, vincristine, Prednisone
[3] Rituximab, Cyclophosphamide, Vincristine, Prednisone
[4] Fludarabine, Cyclophosphamide, Rituximab

Confirmation of efficacy is needed and would be better described by an analysis of the results upon completion of the ongoing randomized controlled trials in indolent NHL.

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 the following indications and is exempt from pediatric study requirements: Follicular lymphoma, Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia, Splenic marginal zone lymphoma, Nodal marginal zone lymphoma, Extranodal marginal zone lymphoma, Chronic lymphocytic leukemia and small lymphocytic leukemia. Zydelig has not been evaluated in pediatric patients.

10. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval

- Risk Benefit Assessment

  Relapsed follicular lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) are serious and life-threatening illnesses. The clinical course for both is characterized by multiple relapses, and there are no curative therapies for multiply-relapsed FL or SLL.

  Zydelig showed a high level of activity (ORR 54% in patients with relapsed FL, and ORR 58% in patients with relapsed SLL) and median duration ranging 0.0+ to 14.7+ months for both indications. The safety profile for Zydelig 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. The efficacy and safety results from clinical trial 101-09 demonstrate an acceptable benefit-risk profile for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies, and for the treatment of patients with relapsed SLL who have received at least two prior systemic therapies.

  Drs. Farrell, DeClaro, Miller and Przepiorka also concluded that there is an acceptable risk-benefit profile for idelalisib in FL and SLL. Furthermore, the review team recommends approval of this application. I concur with this decision.

- 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/

TAMY E KIM
07/21/2014

RICHARD PAZDUR
07/22/2014