CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See stamp date
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205858
Applicant	Gilead Sciences, Inc.
Date of Submission	11 September 2013
PDUFA Goal Date	11 September 2014
Proprietary Name / Established (USAN) names	Zydelig
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:	*Approval*

Material Reviewed/Consulted	Reviewer
Clinical Review	Barry Miller, MS, CRNP / Donna Przepiorka, M.D., Ph.D.
Statistical Review	Kyung Lee, Ph.D. / Lei Nie, Ph.D.
Pharmacology Toxicology Review	Natalie Simpson, Ph.D., Ramadevi Gudi, Ph.D. / Haleh Saber, Ph.D. / John Leighton, Ph.D.
ONDQA-CMC and Biopharmaceutics Reviews	CMC: Debasis Ghosh, Ph.D., M.Pharm (Drug substance)/ Li Shan Hsieh, Ph.D. (Drug product)/Ali Al-Hakim, Ph.D. Biopharm: Sandra Suarez Sharp, Ph.D. /Angelica Dorantes, Ph.D. Microbiology: Jessica Cole, Ph.D. / Bryan Riley, Ph.D. ONDQA: Ramesh Sood, Ph.D. (Tertiary Review)
Clinical Pharmacology Review	DCP V: Stacy Shord, Pharm.D., Julie Bullock, Pharm.D. Pharmacogenomics: Rosane Charlab Orbach, Ph.D. Pharmacometrics: Dhananjay Marathe, Ph.D., Nitin Mehrotra, Ph.D.
OSI/DGCPC	Anthony Orencia, M.D. / Janice Pohlman, M.D., M.P.H.
OSE/DRISK	Naomi Redd, Pharm.D. / Cynthia LaCivita, Pharm.D.
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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. (Applicant) submitted a New Drug Application (NDA) for Zydelig. The Applicant proposed the following indication: 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. In 2008, the WHO Classification of hematologic malignancies removed indolent NHL as a diagnosis in favor of using specific tumor type.

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 non-Hodgkin lymphoma, or indolent NHL. These include chlorambucil, cyclophosphamide, rituximab, ^{90}Y-ibritumomab tiuxetan, and bendamustine. None of the approved therapies are curative for relapsed FL or relapsed SLL. The indications relevant to this application are listed in Table 1.

Table 1 FDA-approved drugs for FL or indolent NHL

Approval	Drug	Oncologic Indication
1957	Chlorambucil	In the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease
1959	Cyclophosphamide	For treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
1997	Rituximab	For the treatment of patients with: Non-Hodgkin's Lymphoma, (b) (4)
2002	^{90}Y-ibritumomab tiuxetan	For the treatment of patients with: relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy
2008	Bendamustine	For treatment of patients with: Chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

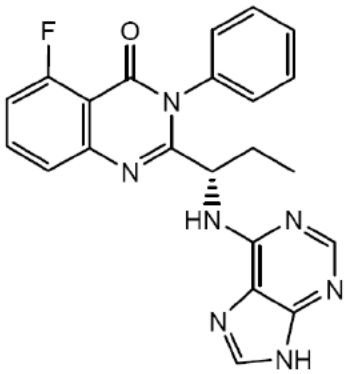
3. CMC/Device

Source: CMC tertiary review

- General product quality considerations

Drug Substance. The drug substance, idelalisib, a new molecular entity, is a (b) (4) It is a white to almost white (b) (4) substance. Idelalisib is designated as a BCS class II with low solubility and high permeability. Idelalisib can exist in two (b) (4) forms, Form I and Form II. (b) (4) is manufactured consistently and used for the manufacture of the drug product. (b) (4) Stability data has been provided which demonstrate that there is no (b) (4). Both forms have comparable solubility and other relevant physical properties. Because of (b) (4) and comparable solubility, the risk of product failure based on drug substance polymorphic form is acceptable. The drug substance synthesis is a (b) (4) synthesis. The structure of the drug substance was adequately established using appropriate analytical techniques.

The chemical name for idelalisib is 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one. It has a molecular formula of C22H18FN7O and a molecular weight of 415.42. Idelalisib has the following structural formula:



Idelalisib is a white to off-white solid with a pH-dependent aqueous solubility ranging from <0.1 mg/mL at pH 5-7 to over 1 mg/mL at pH 2 under ambient conditions.

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the isolated intermediates and the appropriate final drug substance specification. The drug substance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., identification, assay, impurities, enantiomeric purity, particle size distribution, residual solvents, and elemental impurities. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4) months when stored (b) (4)

Drug product. Zydelig (idelalisib) tablets are an immediate release product to be marketed as 100 mg and 150 mg strengths. The drug product formulation uses standard compendial excipients. These are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The manufacturing process includes (b) (4) The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for appearance, identification, assay, (b) (4) uniformity of dosage units, degradation products, dissolution, and microbial controls. All analytical procedures for the drug product are adequately described and validated. 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).

- Facilities review/inspection

  Office of Compliance has issued an overall acceptable recommendation for this application dated 17-May-2014.

Therefore, the NDA is recommended for approval from a CMC perspective.

- Other notable issues (resolved or outstanding)

  At the late cycle meeting on June 5, 2014, the Applicant and the Agency discussed [redacted] (b) (4) of the tablets to allow for [redacted] (b) (4) CMC commented that a CMC supplement can be submitted for [redacted] (b) (4). CMC also referenced the FDA Guidance for Industry on [redacted] (b) (4)

4. Nonclinical Pharmacology/Toxicology

Source: Primary pharmacology-toxicology review

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

  Idelalisib (IDELA; GS-1101; CAL-101), is a kinase inhibitor with selectivity toward PI3Kδ. 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. The primary human metabolite of idelalisib, GS-563117, inhibits lymphocyte-oriented kinase (LOK) and Ste20-like kinase (SLK). According to the information at Cancer Genome Anatomy Project (CGAP), LOK is involved in lymphocyte migration and SLK is involved in apoptosis. GS-563117 is present in the plasma of healthy volunteers at higher levels (62% of drug-related material) than the parent drug (38% of drug-related material) following single oral dosing of idelalisib at 150 mg.

  Idelalisib inhibits PI3K by binding to the ATP binding site of the catalytic subunit p110δ. P110δ is over-expressed in cell lines derived from patients with follicular lymphoma (small cleaved cell lymphoma or NHL). The (IC50) of idelalisib for PI3Kδ was 19 nM in an in vitro assay and the EC50 was 8.9 nM in a cell-based assay. The primary human metabolite, GS-563117, is an inhibitor of LOK and SLK kinases with IC50 values of 0.11 μM and 0.05 μM, respectively. Idelalisib inhibited cell viability and induced apoptosis in malignant B-cells. Idelalisib exhibited higher sensitivity for acute lymphoblastic leukemia (B-ALL) and CLL cells compared with acute myeloid leukemia (AML) and myeloproliferative neoplasm (MPN) cells, suggesting a greater activity potential for B-cell malignancies. Idelalisib inhibited CXCR4 and CXCR5 signaling and chemotaxis in CLL cells, as well as BCR signaling and chemokine secretion and CLL cell migration in an in vitro simulated tumor microenvironment.

  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 increased in the heart weight were observed in the rat in the repeat-dose toxicology studies (see below).

Orally administered idelalisib was absorbed rapidly (T_{max} 0.5 to 2 hours), with bioavailability less than 50% in the animals tested. Idelalisib was localized to most tissues in the rat, but was relatively excluded from bone, brain, spinal cord, and eye lens. In Long-Evans rats, pigmented skin and eye uvea showed higher concentrations of idelalisib than that observed for the similar tissues in Sprague-Dawley rats, suggesting some association of drug-derived radioactivity with melanin. The pharmacokinetics of idelalisib are similar between rats and dogs and humans, however, the plasma level of the metabolite GS-563117 was lower in dogs (34%) and rats (1.4%) than humans (62%). Idelalisib was the most abundant analyte in plasma of rats and dogs (~90% in rats and ~60% in dogs). Idelalisib exhibited moderately high plasma protein binding in all species with the average free fraction values of 19%, 21%, and 16% for rat, dog, and human respectively. The hepatobiliary route was the primary route of excretion within 24 to 48 hours in rats and dogs, with the majority of idelalisib being detected in the feces and 6% or less in the urine.

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 (GI) 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.

An in vitro photo-toxicity study was conducted in the embryonic murine fibroblast BALB/c 3T3 cell line using Neutral Red uptake as a marker of cellular viability in the presence and absence of ultraviolet A (UVA) light exposure. The study was not reviewed by the Agency, however, based on the summary provided by the Applicant, results for idelalisib were inconclusive, while the primary human metabolite, GS-563117, induced photo-toxicity in the presence of UVA exposure.

General toxicology studies were done by the oral route 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

  Idelalisib may impair fertility in humans. In a fertility study, treated male rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated females. Decreased epididymal and testicular weights were observed at all dose levels and reduced sperm concentration at the mid- and high doses; however, there were no adverse effects on fertility parameters. The low dose in males resulted in an exposure (AUC) that is approximately 50% of the exposure in patients at the recommended dose of 150 mg twice daily.

  In a separate fertility study, treated female rats (25, 50, or 100 mg/kg/day of idelalisib) were mated with untreated males. There were no adverse effects on fertility parameters; however, there was a decrease in the number of live embryos at the high dose. The high dose in females resulted in an exposure (AUC) that is approximately 17-fold the exposure in patients at the recommended dose of 150 mg twice daily.

  Reproductive and developmental toxicology studies were conducted in rats to assess the effects of idelalisib on fertility and embryo-fetal development. In a fertility and early embryonic development study, idelalisib-treated male rats were mated to untreated female rats. In this study, idelalisib had no effect on reproductive function or fertility, despite decreased testis and epididymis weights, and reduced sperm counts. When idelalisib-treated female rats were paired with untreated male rats, there was an increase in pre-implantation and post-implantation loss, and early embryo-lethality, resulting in a 20% decrease in the number of live embryos at the high dose of 100 mg/kg (600 mg/m^2).

  The embryo-fetal development effects of idelalisib were studied in the rat. Idelalisib produced post-implantation loss and was teratogenic. Idelalisib was maternally toxic based on reductions in net body weight gain > 10% at the mid and high doses (75 and 150 mg/kg/day; 450 and 900 mg/m^2/day) and clinical signs of maternal toxicity, most evident at the high dose. Adverse embryo-fetal findings at doses ≥ 75 mg/kg/day (450 mg/m^2/day) included decreased fetal weights, external malformations (short tail) and skeletal variations (delayed ossifications and/or unossification of the skull, vertebrae, and sternebrae). At 150 mg/kg/day (900 mg/m^2/day) dose, idelalisib resulted in spontaneous abortion (urogenital loss, complete resorption, increased post-implantation

loss, and reduced mean litter size) and malformations (vertebral agenesis with anury, microphthalmia, anophthalmia, and hydrocephaly) in live fetuses. The dose of 75 and 150 mg/kg/day of idelalisib in rats resulted in exposures (AUC) of approximately 25 and 60 times, respectively, the human exposure at the recommended dose of 150 mg BID.

As a kinase inhibitor, the teratogenic effects of idelalisib were expected and observed in rats at the mid and high doses tested. Based on teratogenicity findings, an embryo-fetal developmental study in a second species is not needed and pregnancy category D is recommended.

- Other notable issues (resolved or outstanding)

  There are no outstanding issues with nonclinical pharmacology and toxicology.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical pharmacology primary review

- General clinical pharmacology and biopharmaceutics considerations

  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.

  Is the proposed starting dose of 150 mg BID reasonable? Yes. The maximum administered dose (MAD) was 350 mg BID and no maximum tolerated dose (MTD) was identified in the dose escalation phase. No exposure-response (E-R) relationships were observed for the primary endpoints in the NHL (101-09) and CLL (312-0116) trials and for selected safety endpoints, except for diarrhea in the NHL population. In these trials most patients administered a dose of 150 mg BID achieved minimal concentrations (C_{tau}) greater than the in vitro EC_{90} for PI3Kδ inhibition. A lower starting dose is not recommended, because the ER relationship with tumor size in the dose finding study (101-02) suggests that the lowest exposure is associated with less

clinical activity. A higher starting dose is not recommended as idelalisib is associated with hepatotoxicity and higher exposures were associated with a greater incidence of diarrhea.

- 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) $\geq$ 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

Nonclinical. The IC_{50} for the hERG potassium current was estimated to be greater than 50 μM (BHR00004). No effects on electrocardiograms (ECGs) were observed in dogs treated with doses up to 20 mg/kg. The no observed adverse effect level (NOAEL) is 20 mg/kg (BHR00041).

Clinical (Thorough QT 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 Microbiology

The application did not include clinical microbiology information. Refer to Section 8 regarding infections in Zydelig-treated patients.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the clinical efficacy reviewer (Barry Miller) and statistical reviewer (Kyung Lee) on the efficacy of Zydelig for the following recommended indications:

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

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).

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%),

[1] Bendamustine, Rituximab

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 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.

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.

8. Safety

I agree with the clinical safety reviewer's (Donna Przepiorka) conclusion regarding the safety of Zydelig.

Safety Summary

The final safety dataset included 354 adults with hematological malignancies treated with idelalisib as monotherapy in Phase 1 or Phase 2 trials. The original submission of the NDA included data for only 352 subjects, and it was this original dataset that was used for the initial assessment in the full monotherapy safety population. Of these 354 subjects, 146 were treated with idelalisib 150 mg BID for INHL (INHL 150 mg BID subgroup). Median time on study for the INHL 150 mg BID subgroup was 6.1 months (range, 0.3-26.4 months). The safety dataset also included information for 300 volunteers without hematological malignancies (18 of whom received only placebo) for studies of pharmacokinetics and drug-drug interactions.

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

The study population was monitored for deaths, serious adverse events, adverse events of interest, common adverse events and common laboratory tests. A thorough QT study was conducted. There are no safety data in children.

Analysis of the full monotherapy safety population showed:

- Sixty-one deaths were reported. The root causes of death were progressive disease for 36 (59%) subjects, infection for 17 (28%) subjects, and other adverse event for 8 (13%) subjects.
- Seven deaths were considered at least possibly related to idelalisib. The fatal events included infection with neutropenia, sudden death, respiratory failure, tumor lysis syndrome, and enteropathy.
- Increases in transaminases, neutropenia and nausea appeared to be dose-related with the highest incidences in subjects treated with idelalisib 350 mg BID.
- There were three cases with transaminase and bilirubin elevations consistent with Hy's law, but concomitant use of other hepatotoxic drugs confounded the analysis.

Significant findings from analysis of the INHL 150 mg BID subgroup included:

- An SAE (serious adverse event) was reported for 74 (51%) subjects. The most common SAEs were pneumonia (16%), diarrhea (11%), and pyrexia (10%). The SAEs were considered related for 44 (30%) subjects.
- Adverse events of special interest considered related to use of idelalisib by history, rechallenge and/or biopsy included transaminase elevation, diarrhea/colitis, rash, and pneumonitis. The actual rate of drug-induced pneumonitis was difficult is discern due to the high background rates of infections in this population.
- An AE (adverse event) resulted in drug interruption or permanent withdrawal for 80 (55%) subjects.
- A TEAE (treatment-emergent adverse event) was reported for 99% of the subjects. The TEAEs reported most frequently (>20%) were diarrhea (47%), fatigue (34%), cough (30%), nausea (29%), pyrexia (29%), neutropenia (27%), elevated transaminases (26%), pneumonia (25%), rash (23%), and abdominal pain (23%).
- The incidence of TEAEs was not affected by gender, age or race. There was also no consistent difference by the type of lymphoma. There was a trend for an increase in diarrhea, nausea, neutropenia, anemia and asthenia in subjects <55 kg in weight. There was also a trend for an increase in diarrhea when idelalisib was used concurrently with a proton pump inhibitor, although pharmacokinetics studies demonstrated this did not result from a drug-drug interaction.
- A grade $\geq$3 TEAE was reported for 64%. The grade $\geq$3 TEAEs reported most frequently (>10%) were neutropenia (21%), elevated transaminases (17%), pneumonia (16%) and diarrhea (14%).

- The most common grade ≥3 laboratory abnormalities were neutropenia (27%), ALT increased (18%), AST increased (12%) and thrombocytopenia (9%). Hypogamma-globulinemia occurred in a small percentage of subjects in whom it was not pre-existing due to the underlying disease or prior treatment.

The safety profile was similar in the healthy volunteer studies, confirming that the toxicities seen were related to idelalisib.

Overall, the safety profile of idelalisib 150 mg BID was marked by substantial toxicity. Although much of the toxicity was self-limited when the drug was discontinued, safe use of idelalisib will require detailed labeling with adequate warnings, instructions for monitoring, and instructions for dose modifications. Given that follow-up for the majority of the study subjects was relatively short, the data were not sufficient to confirm safety of long-term use. Additional characterization of idelalisib-related pneumonitis is needed.

9. 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 on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

10. Pediatrics

Zydelig is exempt from the pediatric study requirements in 21 CFR 314.55. Zydelig was granted Orphan Drug Designation by the Office of Orphan Products Development for the following indications (date granted):

- Follicular lymphoma (September 26, 2013)
- Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia (September 26, 2013)
- Splenic marginal zone lymphoma (October 15, 2013)
- Nodal marginal zone lymphoma (October 15, 2013)
- Extranodal marginal zone lymphoma (October 15, 2013)
- Chronic lymphocytic leukemia and small lymphocytic leukemia (October 15, 2013)

Zydelig has not been evaluated in pediatric patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.

- **Financial Disclosures:** No issues. The Applicant provided a list of clinical investigators and financial disclosures for the pivotal and supporting clinical trials. None of the disclosures submitted revealed a potential conflict of interest.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** The following is from the overall assessment of findings and general recommendations:

  Two domestic clinical sites were selected for inspection of Study 101-09 supporting this NDA: Ajay Gopal, M.D. (University of Washington, Fred Hutchinson Cancer Research Center) and Peter Martin, M.D (Weill Cornell, New York Presbyterian Hospital). The Applicant (Gilead Sciences, Inc.) was also inspected.

  The classification for Dr. Martin is NAI (No Action Indicated). The preliminary classification for Dr. Gopal and Gilead Sciences is VAI (Voluntary Action Indicated).

  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.
- **Other discipline consults**: None
- **Other outstanding regulatory issues**: None

12. Labeling

- **Proprietary name.** On 3 October 2013, OSE/DMEPA concluded that the proposed proprietary name, Zydelig was conditionally acceptable.

- **OSE/DRISK.** DRISK and Division of Hematology Products have determined, if Zydelig is approved, a REMS (Risk Evaluation and Mitigation Strategy) that consists of a communication plan to address the risks of hepatotoxicity, intestinal perforation, colitis, and pneumonitis will be necessary to ensure that the benefits outweigh the risks of treatment. The Agency instructed the Applicant to submit a risk management plan that includes a proposed communication plan REMS.

  The Applicant submitted the proposed REMS including REMS materials and REMS supporting document on 21 May 2014. An amended version was submitted on 28 May 2014. In general, DRISK evaluation noted that the outline and layout of the proposed REMS, REMS Supporting Document, and REMS communication materials (REMS letter to healthcare providers, REMS letter to professional societies, REMS Fact sheet, REMS journal information piece, and REMS website) were acceptable. However, significant revisions to the language for these materials are needed based on the final version of the labeling.

- **OSE/DMEPA.** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

- **Patient Labeling Team.** The patient labeling group participated in the labeling discussions and reviewed the Medication Guide.

- **OPDP.** OPDP attended labeling meetings and provided input. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

13. 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.

  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 small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. All review team members recommend approval.

  However, although 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 following issues in the efficacy results are more supportive of accelerated approval rather than regular approval.

  There is uncertainty as to the relation of ORR and DOR to ultimate outcome (overall survival). Majority of the responses consisted of partial responses. The complete response rates were 8% and 0% in the population of patients with relapsed FL and relapsed SLL, respectively. The durability of the responses is also limited by the lack of confirmed responses[5] in 23% (9/39) and 27% (4/15) of the responders in the relapsed FL and relapsed SLL populations, respectively. Finally, there were only 33 patients treated for more than 6 months, which limits the ability to describe continued efficacy of Zydelig for the treatment 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

[5] ORR maintained ≥ 2 consecutive assessments >2 months apart

perforation. Additional items in Warnings and Precautions include severe cutaneous reactions, neutropenia, and embryo-fetal toxicity. A Medication Guide will be required.

The above toxicities were likely moderated in part by close monitoring and dose interruption and/or reduction for toxicities, a strategy that would be needed for safe use of the drug in practice. It is not clear that this can be accomplished with an oral medication without explicit instructions to the patients and education of the healthcare providers. Hence, the Applicant was required to submit a REMS communication plan to address the risks of hepatotoxicity, intestinal perforation, colitis, and pneumonitis. The REMS will be necessary to ensure that the benefits outweigh the risks of treatment.

The occurrence of significant toxicities with short (less than 6 months) duration of idelalisib treatment is concerning. Alternative dosing regimens for idelalisib will need to be explored

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  As discussed above, the approval for this application will include a REMS communication plan. The final elements of the REMS are under negotiation: REMS letter to healthcare providers, REMS letter to professional societies, REMS Fact sheet, REMS journal information piece, REMS website, and a Patient Safety Information Card.

  Refer to the DRISK reviews for the final elements and details of the REMS.

- Recommendation for other Postmarketing Requirements and Commitments

  I agree with the following postmarketing requirements proposed by the review teams, and agreed upon with the Applicant. PMR 2180-1, 2180-2, and 2180-3 are efficacy PMRs (Subpart H). PMRs 2180-4 to 2180-7 represent safety PMRs.

  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.

- Recommended Comments to Applicant

  None

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

/s/

ROMEO A DE CLARO
07/07/2014