

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208573
PDUFA Goal Date	June 29, 2016
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Reviewer Name(s)	Mona Patel, Pharm.D., Senior Risk Management Analyst
DRISK Team Leader	Naomi Redd, Pharm. D., Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	March 14, 2016
Subject	Evaluation to determine if a REMS is necessary
Established Name	venetoclax
(Proposed) Trade Name	Venclexta
Applicant	Abbvie Inc.
Therapeutic Class	B-cell lymphoma-2 (Bcl-2) protein inhibitor
Formulation(s)	Oral tablet
Dosing Regimen	400 mg daily
Proposed Indication(s)	Chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Venclexta® (venetoclax) is necessary to ensure the benefit of this product outweighs its risk. Abbvie Inc. submitted a New Drug Application (NDA) 208573 for Venclexta (venetoclax) for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion. The risks associated with the use of venetoclax are tumor lysis syndrome and neutropenia. The applicant did not submit a REMS with this application but submitted a Medication Guide and a proposed pharmacovigilance plan.

DRISK and the Division of Hematology Products agree that a REMS is not needed to ensure the benefits of venetoclax outweigh its risks. The risks seen with this drug will be communicated through labeling.

1 Introduction

Abbvie Incorporated submitted a New Drug Application (NDA 208573) for venetoclax with the proposed indication for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion (17p del), as detected by an FDA approved test, who have received at least one prior therapy. This application is under review in the Division of Hematology Products. The applicant did not submit a REMS with this application but proposed risk minimization measures that included product labeling, a Medication Guide and an enhanced pharmacovigilance plan for the drug.

2 Background

2.1 PRODUCT INFORMATION¹

Venclexta (venetoclax) is a new molecular entity, first-in-class B-cell lymphoma-2 (Bcl-2) protein inhibitor in the biarylacetylsulfonamide chemical class that could restore programmed cell death (apoptosis) in cancer cells. The sponsor proposed the following indication: treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion. FDA revised the indication to be for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p del, as detected by an FDA approved test, who have received at least one prior therapy. The proposed dosing schedule for patients with CLL is initiation of therapy with venetoclax at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule (50 mg for 7 days, then 100 mg for 7 days, then 200 mg for 7 days), followed by the recommended daily dose of 400 mg. The dosage form is oral tablets provided at strengths of 10 mg, 50 mg, and 100 mg. It contains four weekly wallet blister packs: week 1 (14 x 10 mg tablets), week 2 (7 x 50 mg tablets), week 3 (7 x 100 mg tablets), and week 4 (14 x 100 mg tablets). Once the ramp-

¹ Clinical Overview (section 2.5), venetoclax

up period is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles. This is a NME 505 (b)(1) application that was granted Breakthrough Therapy designation for 17p del relapse or refractory (r/r) CLL, has Orphan Drug status, and is under Priority review with a Prescription Drug User Fee Act date of June 29, 2016. The efficacy of the product is based upon pivotal study M13-982. Venetoclax is not licensed in the United States; however, according to the applicant, an application for marketing authorization has been made to the European Union and other global jurisdictions.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208573 relevant to this review:

- 11/29/2010: IND 110159 active
- 9/20/2012: Orphan designation granted for CLL
- 4/27/15: Breakthrough Therapy Designation granted for 17p del R/R CLL
- 9/15/2015: Part 1 Rolling Submission Received (CMC & Nonclinical Modules)
- 10/29/2015: Part 2 Rolling Submission Received (Administrative, Summary, and Clinical Modules)
- 12/11/2016: Applicant Orientation Presentation
- 1/27/2016: Midcycle Meeting
- 2/8/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for venetoclax
- 2/29/16: Late Cycle Meeting

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chronic lymphocytic leukemia (CLL) represents about 25% of the new cases of leukemia. The American Cancer Society estimates that in 2015, there will be about 14,620 new cases of CLL and about 4,650 deaths from CLL. CLL primarily affects elderly individuals. The average age at diagnosis is around 71 years old.² According to the National Cancer Institute's Surveillance, Epidemiology, and End Results database, between 2005-2011, in the United States, the 5 year survival rate for patients diagnosed with CLL was 81.7% with a median age at death for CLL of 79 years old.³

² <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-key-statistics> accessed on 2/8/15

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Rituxan (rituximab) and Gazyva (obinutuzumab) are CD-20 directed cytolytic antibody drugs approved by the FDA in 1997 and 2013 respectively for first-line treatment of CLL. Imbruvica (ibrutinib), approved in 2013, and Zydelig (idelalisib), approved in 2014, are kinase inhibitors to treat (b) (4) CLL. Both CD-20 directed cytolytic antibody treatments contain a Boxed Warning and one of the kinase inhibitors, idelalisib, contains a communication plan REMS to inform healthcare providers of the following fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, and intestinal perforation.

The table in Appendix 1 summarizes these treatment modalities.

These available treatments used to treat patients with CLL or those who have relapsed are associated with significant toxicities such as increased risk of serious infections including opportunistic infections and significant bone marrow suppression or both. Of these agents listed in Table 1, ibrutinib is the only drug also indicated for treatment of patients with 17p del CLL. Overall response rate was 47.6% in those patients treated with ibrutinib (all partial remission [PR]; none were complete response CRs).⁴ Also in 2014, the combination of idelalisib + rituximab was approved by the FDA for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other comorbidities.

The recent approval of ibrutinib and idelalisib represent a change for patients with either 17p del or r/r CLL. These agents provide disease control of similar or greater duration when compared to previous therapies with alternative, if not improved safety profiles. However, these newer agents have limitations and liabilities including low CR rates and toxicities that require close monitoring throughout therapy (in the case of idelalisib, risk mitigation measures beyond labeling that include a REMS), or that may exclude certain patient populations.

There remains a substantial unmet medical need for treatments that improve response, maintain remission, provide a more favorable safety profile and achieve long-term control of CLL, including those patients harboring the 17p del mutation and those refractory to initial treatment. While significant advances have been made in the treatment of patients with CLL, it still remains largely an incurable disease. There is a current unmet need for treatments that improve response, maintain remission, provide a more favorable safety profile, and achieve the long-term control of CLL with optimal quality of life.

4 Benefit Assessment^{5,6,1}

³ <http://seer.cancer.gov/statfacts/html/clyl.html> accessed on 2/8/15

⁴ Imbruvica (ibrutinib) US Package Insert (1/2015)

⁵ Venclexta (venetoclax) draft label, February 25, 2016

The evidence of clinical benefit for venetoclax in relapsed/refractory CLL patients is based upon pivotal study M13-982. Study M13-982 is a Phase 2, open-label, multicenter, study evaluating the efficacy of venetoclax in relapsed/refractory or previously untreated patients with CLL harboring 17p del that includes the TP53 locus. One hundred and seven patients were enrolled in this study, identified using Vysis CLL FISH Probe Kit, and dosed at 400 mg after the initial 5-week ramp-up starting at 20 mg.

Patients enrolled in this study had a median age of 67 years. Close to 97% of patients were white, 65.4% were male, and ECOG performance status of 0 was 39.3%, 52.3% for ECOG of 1, and 8.4% for ECOG of 2. The median number of prior therapies was 2. The median time on treatment with venetoclax was 12.1 months. The primary endpoint was overall response rate (ORR) which was assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Overall response rate was 79.4%. Secondary endpoints were complete response (7.5%) and partial response (69.2%). The results were clinically meaningful and statistically significant.

5 Risk Assessment & Safe Use Conditions⁵

The safety of single agent venetoclax at the 400 mg recommended daily dose following an initial 5 week dose ramp-up schedule was evaluated in 240 patients with previously treated CLL, including 160 patients with 17p del, in 3 open-label, non-randomized trials (Study M13-982, M12-175, and M14-032). Adverse event data was summarized by system organ classes (SOCs) and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Serious adverse reactions were reported in 43.8% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia, anemia, and TLS.

5.1 Serious Adverse Reactions/ Severe Adverse reactions (> Grade III)

Tumor Lysis Syndrome (TLS)-In the initial Phase 1 dose-finding trial, the incidence of TLS was 12%, including 2 fatal events and 3 events of acute renal failure, 1 of which required dialysis. Lengthening the ramp-up phase over 5 weeks and decreasing the starting dose to 20 mg resulted in 6% of 66 patients with CLL to have TLS. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax and at each dose increase. Withholding the next day's dose helped to decrease the risk of TLS. If blood chemistry resolved within 24-48 hours of the last dose, dosing could resume at same dose. For any blood chemistry changes requiring more than 48 hours to resolve, dose was to be resumed at a reduced dose (i.e., 400 mg dose \rightarrow restart at 300 mg, see Table 3 from USPI for dose modification table). Prophylactic hydration and anti-hyperuricemics (i.e., allopurinol) prior to initiation of the first dose of venetoclax was recommended to help reduce the risk

⁶ January 27, 2016 Midcycle Slides by Lori Ehrlich

of TLS. Patients were advised to stay hydrated while on drug therapy with ~6-8 glasses of water each day. Tumor burden assessments, radiographic evaluation (e.g., CT scan), blood chemistry assessment (creatinine, uric acid, potassium, phosphorus, and calcium), and correction of pre-existing abnormalities within 72 hours prior to initiation of treatment could help reduce the risk for TLS. Chemistry evaluation should be performed at hour 0, 8, and 24 hours after the first dose of venetoclax and at 20 mg and 50 mg doses.

Neutropenia-Grade 3 or 4 neutropenia occurred in 40.8% of patients treated with venetoclax. Dosing was to be interrupted or reduced for severe neutropenia. Granulocyte-colony stimulating factor (G-CSF) could be administered with venetoclax if clinically indicated. For the first occurrence of a Grade 3 or 4 neutropenia with infection or fever, once the toxicity resolved to Grade 1 or baseline level, venetoclax could be resumed at the same dose. For second and subsequent occurrences, venetoclax therapy could be interrupted. After resolution of neutropenia, resume a reduced dose according to Table 3 of the USPI (i.e., 400 mg → 300 mg). Permanent discontinuation should be considered for patients who require dose reductions to less than 100 mg for more than 2 weeks. Complete blood counts should be monitored throughout the treatment period.

Not administering live attenuated virus vaccines during or after treatment with venetoclax until B-cell recovery occurs will also be included under the Warnings & Precautions section of the labeling. Additionally, there are no available human data informing drug-associated risk on the fetus. Based on toxicity observed in mice, venetoclax may have effects on the fetus when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on AUC at the recommended human dose of 400 mg daily.⁵ Therefore, women are to be advised of the potential risk of fetal toxicity. It is also advised that patients avoid consuming grapefruit products, Seville oranges, or starfruit during treatment. Patients are also to be advised that venetoclax may interact with some drugs (i.e., strong CYP3A inhibitors) at initiation and during the ramp-up phase and are advised to inform their healthcare provider of the use of any prescription medication, over-the-counter drugs, vitamins and herbal products. Mild to moderate renal or hepatic impairment does not appear to impact venetoclax clearance.

It should be noted that in patients treated with single-agent venetoclax, 10.0% (29/289) of patients discontinued venetoclax for Richter's transformation. Thirteen of those reports of Richter's were within 6 months of initiating venetoclax which could indicate that the Richter's transformation could have initiated prior to starting the drug. The rate of Richter's transformation in patients treated with single-agent venetoclax is within the expected rate of Richter's transformation in patients with CLL, though this warrants ongoing monitoring.⁷

6 Analysis of Expected Postmarket Use

⁷ Draft clinical review by Dr. Lori Ehrlich (v. March 1, 2016)

Venetoclax will be administered in both the inpatient and outpatient setting by practicing hematologists who are familiar with the risks and have an important role in managing the risks. It is recommended more intensive measures such as intravenous hydration and hospitalization for patients at increased risk for developing TLS be employed. The safe use conditions proposed in the labeling are consistent with other products with similar risks. In terms of usability, the human factors study results demonstrated that the venetoclax starting pack could be used safely and effectively by users as the majority of participants on the study were able to use the product as intended without any failures.⁸ Furthermore, with the use of the Medication Guide, patients and caregivers could reliably recognize symptoms with the risk of TLS and take the necessary actions to manage the risk

7 Risk Management Activities Proposed by the Applicant

Abbvie did not propose any risk management activities for venetoclax beyond routine measures. Abbvie states that the “proposed labeling and routine reporting/pharmacovigilance are sufficient to mitigate the risks and preserve the benefits in the treatment of r/r CLL with 17p del. Abbvie does not propose a Boxed Warning in the labeling. They do propose a Medication Guide to be dispensed with each prescription.

8 Discussion of Need for a REMS

Despite the available chemotherapy options, there remains a substantial unmet medical need for treatments that improve response, maintain remission, provide a more favorable safety profile and achieve long-term control of CLL, including those patients harboring the 17p del mutation and those refractory to initial treatment. The indication for venetoclax is for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p del, as detected by an FDA approved test, who have received at least one prior therapy.

The anticipated duration of use for venetoclax is an initial weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg to be taken until disease progression or unacceptable toxicity.

Approved first-line treatment options in the US for CLL include obinutuzumab and rituximab. Second-line treatment options approved for CLL patients include ibrutinib and idelalisib.

The adverse events of concern with venetoclax were TLS and neutropenia. In order to minimize the risk of patients having TLS, the label states that patients should be assessed for level of risk and provided prophylactic hydration and started on anti-hyperuricemics (i.e., allopurinol) prior to the first dose of venetoclax. The Division determined these events to be adequately addressed under the Warnings & Precautions section of the label. In comparison with other agents for the treatment of CLL, venetoclax appeared to have fewer side effects that rose to the level of a Boxed Warning or even the Warnings & Precautions section of the label.

⁸ Human Factors Review by Nicole Garrison (January 27, 2016)

TLS has occurred with venetoclax, obinutuzumab and ibrutinib. All of these drugs required a Warnings and Precautions, but only obinutuzumab required a Boxed Warning. In addition to TLS, neutropenia was included in the labeling under Warnings & Precautions for venetoclax as was also seen in the labeling for obinutuzumab and idelalisib; however, neutropenia was more of a concern with obinutuzumab as it rose to the level of a Boxed Warning for the drug. Idelalisib was the only drug for CLL which required a REMS (communication plan) to inform healthcare providers of risks associated with fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, and intestinal perforation.

The efficacy of venetoclax for patients with r/r CLL is compelling for accelerated approval for only the r/r CLL population with 17p del. It is another treatment option for the r/r CLL with 17p del. In the pivotal study M13-982, the overall response rate was 79.4%. The result was considered clinically meaningful and statistically significant.

The likely prescribing population for venetoclax will be hematologists who are familiar with the disease and adverse events seen with drugs used for the treatment of CLL with 17p del.

9 Conclusion & Recommendations

Based on the available data, anticipated prescribing population, and patient population for use of this drug, DRISK and DHP agree that the benefit-risk profile is acceptable and a REMS is not necessary for venetoclax to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

Appendix 1

Table 1: Summary of Approved Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic),	Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
rituximab (Rituxan) ⁹	1997	In combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia	Cycle 1: 375 mg/m ² ; Cycle 2-6: 500 mg/m ² , in combination with fludarabine and cyclophosphamide	<i>Fatal Infusion Reactions; Severe mucocutaneous reactions; Hepatitis B Virus Reactivation; Progressive Multifocal Leukoencephalopathy</i>	<i>Boxed Warning</i> Medication Guide
Ofatumumab (Arzerra) ¹⁰	2009	In combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia for whom fludarabine-based therapy is considered inappropriate;	300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses.	<i>Hepatitis B virus reactivation</i> <i>Progressive multifocal leukoencephalopathy</i>	<i>Boxed Warning</i>

⁹ Rituxan (rituximab) US Package Insert (8/2014)

¹⁰ Arzerra (ofatumumab) US Package Insert (1/2016)

		for extended treatment of pts who are in complete or partial response after at least 2 lines of therapy for recurrent or progressive CLL; for the treatment of patients with CLL refractory to fludarabine and alemtuzumab			
alemtuzumab (Campath) ⁴	2001	Single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)	Escalate to recommended dose of 30 mg/day three times per week for 12 weeks	<i>Cytopenias, Infusion Reactions, and Infections</i>	<i>Boxed Warning</i> *no longer marketed as of 09/04/12, but available to cancer patients free through the US Campath Distribution Program.
obinutuzumab (Gazyva) ⁵	2013	in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia	100 mg on day 1 Cycle 1 900 mg on day 2 Cycle 2 1000 mg on day 8 and 15 of Cycle 1 1000 mg on day 1 of Cycles 2-6	<i>Hepatitis B Virus (HBV) reactivation; Progressive Multifocal Leukoencephalopathy (PML); Tumor Lysis Syndrome; Infections; Neutropenia; Thrombocytopenia;</i>	<i>Boxed Warning</i>
ibrutinib (Imbruvica) ⁴	2013	Chronic lymphocytic leukemia who have received at least one	420 mg taken orally once daily	Hemorrhage, infections, cytopenias, atrial fibrillation, second primary malignancies, tumor lysis syndrome,	Patient Information

⁴ Campath (alemtuzumab) US Package Insert (9/2014)

⁵ Gazyva (obinutuzumab) US Package Insert (9/2015)

		prior therapy; CLL with 17p deletion		embryo-fetal toxicity	
Idelalisib (Zydelig) ⁶	2014	For the treatment of 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	150 mg orally, twice daily	<i>Fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, and intestinal perforation;</i> severe cutaneous reactions, anaphylaxis, neutropenia, embryo- fetal toxicity	REMS; <i>Boxed Warning</i>

⁶ Zydelig (idelalisib) US Package Insert (7/2014)

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/s/

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03/15/2016

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