

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208573Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	208573
Applicant	AbbVie, Inc.
Date of Submission	Rolling Submission Final 10/29/15
PDUFA Goal Date	06/29/16
Proprietary / Non-Proprietary Name	Venclaxta / venetoclax
Dosage form(s) / Strength(s)	Tablets / 10, 50, and 100 mg
Regulatory Action	Accelerated Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Division Director	Ann Farrell, MD
Medical Officer Review	Lori Ehrlich, MD, PhD/Virginia Kwitkowski, BSN, MS, ACNP-BC
Regulatory Health Project manager	Beatrice Kallungal, BS, MS
Statistical Review	Qing Xu, PhD/Yuan-Li Shen, DrPh
Pharmacology Toxicology Review	Ramadevi Gudi, PhD/ Emily Place, PhD/Christopher Sheth, PhD/John Leighton, PhD
OPQ Review	Rajiv Agarwal/Monica Cooper/Gerlie Gieser/Ruth Moore /Tracey Rogers, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Guoxiang Shen, PhD/Lian Ma, PhD/Justin Earp, PhD/Sarah Dorff, PhD/Bahru Habtemariam, PharmD/Nitin Mehrotra,
OPDP/DMPP/DMEPA	Nisha Patel, PharmD/ Rowell Medina, PharmD /
OSI	Anthony Orencia MD, FACP, Janice Pohlman MD, MPH
CDTL Review	Virginia Kwitkowski, BSN, MS, ACNP-BC
OSE/DEPI	None
OSE/DMEPA/OMP/OPDP	Kevin Wright/Nicole Garrison, PharmD, BCPS/Yelena
OSE/DRISK	Mona Patel, PharmD/Naomi Redd, PharmD/Cynthia LaCivita, PharmD
Other	Dinko Rekić/Jiang Liu/Huifang Chen/Qianyu Dang/Michael Li/ Norman L Stockbridge, MD

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Venetoclax is an orally available, small molecule inhibitor of BCL-2 (B-cell lymphoma protein 2) that has been studied in patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL), including those with the 17p deletion, which is typically less responsive to treatment than those without this gene deletion. The Applicant has submitted data from single-arm studies that demonstrate that the overall response rate (with durability of response) is higher than the available therapy (ibrutinib) for patients with the 17p deletion.

There are an estimated 15,000 new cases of CLL per year in the United States. CLL occurs primarily in the elderly. Patients with CLL and the 17p deletion have a very poor prognosis, with survival duration of less than 2 years. There is only one drug approved at this time, specifically for this 17p deletion subset. This drug is ibrutinib (Imbruvica) and in a similar patient population with 17p deletion, it had a 48% Overall Response Rate (ORR).

The efficacy of venetoclax for the treatment of R/R CLL with 17p deletion was evaluated in a single-arm, phase 2 trial, M13-982. The ORR in patients with 17p del in this trial was 80.2% with a complete response rate of 7.5%. ORR is a surrogate endpoint in CLL for progression-free and overall survival (OS). Venetoclax demonstrates an improvement over available therapies in patients with 17p deletion, and is eligible for accelerated approval.

(b) (4)

The recommended dose of venetoclax is 400 mg daily that is achieved by a lower starting dose followed by a ramp-up, to reduce the risk of a life-threatening condition called tumor lysis syndrome (TLS). Patients who take venetoclax will be evaluated for their specific risk of TLS, and hydrated (with oral or intravenous fluids) and given medications that reduce their uric acid levels, in addition to slowly increasing the dose to the target dose of 400 mg daily. Close monitoring of their blood tests will be needed during the early treatment to detect cases of TLS.

The most frequent (>25%) Adverse Reactions in patients with R/R CLL were neutropenia (39%), diarrhea (35%), nausea (33%), and anemia (28%).

Venetoclax represents an additional oral therapeutic agent with a novel mechanism of action for the treatment of patients with relapsed or refractory CLL with 17p deletion. The efficacy of venetoclax for the treatment of patients with R/R CLL with the 17p deletion is supported by a surrogate endpoint of ORR. The higher response rate for venetoclax over ibrutinib represents an improvement over available therapies. The safety in patients with R/R CLL is acceptable with rigorous management of the risk of tumor lysis syndrome which are addressed through labeling. Venetoclax is an important addition to the treatment armamentarium for patients with R/R CLL with 17p deletion. The risk-benefit profile was also discussed by Drs. Farrell, Kwitkowski and Ehrlich, all review team members recommend approval of this application, and I concur. This application will be given accelerated approval for the following indication: "For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • CLL is a cancer of mature B lymphocytes, a type of white blood cell, which affects blood, bone marrow, lymph nodes, or spleen. • Approximately 15,000 new cases occur per year, predominantly in older adults with about 70% occurring in patients older than 65 years. • CLL is typically a slowly progressing disease, and the percentage of patients surviving at 5 years is 81.7%. • The 17p gene deletion is an ultra-high risk poor prognostic factor that is more common in patients with relapsed or refractory disease. The median duration of survival for patients with 17p deletion is generally less than 24 months. 	<p>Relapsed or refractory CLL with 17p deletion is serious, life threatening, and rare in frequency. The duration of survival for patients with 17p deletion is poor. Relapsed or refractory CLL generally affects the elderly.</p>
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • For patients with relapsed or refractory CLL, treatment decisions are based on a patient's response to prior chemo- or chemoimmunotherapy, age, and presence of significant comorbidities. • FDA-approved therapies for the treatment of relapsed or refractory CLL include combination chemo-immunotherapy (fludarabine, cyclophosphamide, rituximab), ibrutinib, idelalisib with rituximab, and ofatumumab. • The response rates to standard therapies for patients with 17p deletion are significantly lower. • The only FDA-approved therapy for the treatment of patients with 17p deleted CLL is ibrutinib. 	<p>The standard of care for relapsed or refractory CLL is variable and can include re-treatment with a prior therapy though each successive treatment usually results in shorter response durations. Despite several new approvals for relapsed or refractory CLL, the disease remains incurable for most patients, and as such is an unmet medical need.</p> <p>The response rates in patients with 17p deletion are lower and the available therapies are much more limited.</p>
<p>Benefit</p>	<ul style="list-style-type: none"> • The Phase 2, single-arm trial, M13-982, was venetoclax for the treatment of patients with relapsed or refractory CLL harboring the 17p deletion. The trial included 107 patients, and 106 patients had 17p deletion. • The primary endpoint was the ORR in the first 70 patients enrolled, but the response rate was evaluated for all patients enrolled. A response rate of >40% was considered clinically meaningful based on response rates to available therapies. • The ORR in 106 patients with 17p deletion was 80.2% (95% CI: 71.3, 87.3) with a complete remission rate of 7.5% (95% CI: 3.3, 14.3). • The phase 1, dose-escalation trial, M12-175, was venetoclax for the treatment of patients with relapsed or refractory CLL. This trial was designed to evaluate the safety of venetoclax and to determine the recommended phase 2 dose. As such, the study was not powered to evaluate efficacy, and all efficacy evaluations were considered exploratory. The trial included 57 patients with relapsed or refractory CLL treated at the target dose of 400 mg daily. <p style="text-align: right;">(b) (4)</p>	<p>The phase 2 trial in patients with relapsed or refractory CLL with 17p deletion met the primary endpoint of ORR. In this patient population, venetoclax is an improvement over available therapy with a better response rate and demonstration of complete responses which were not seen with ibrutinib. ORR is considered a surrogate endpoint for progression-free or overall survival in CLL. Therefore, venetoclax is recommended for accelerated approval for patients with 17p deletion.</p> <p style="text-align: right;">(b) (4)</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		(b) (4)
<p>Risk</p>	<ul style="list-style-type: none"> • Approximately 500 patients with cancer have been treated with venetoclax either as a single agent or in combination with other therapy. • In patients with CLL treated with single-agent venetoclax, 289 patients have been exposed with 240 patients exposed at the proposed target dose of 400 mg. • Although most patients treated with venetoclax had a treatment-emergent adverse reaction, only about 10% discontinued venetoclax due to an adverse reaction other than disease progression. Generally, the pattern of adverse reactions reflects events expected for a heavily pre-treated elderly population with R/R CLL with the exception of on-target effects of tumor lysis syndrome and neutropenia. • The risk assessment and prophylaxis for tumor lysis syndrome was modified in two major amendments to the venetoclax protocols. The dosing regimen for venetoclax was adjusted to include a ramp-up phase. The final estimated risk of tumor lysis syndrome was 6% and all events were limited to laboratory findings with limited clinical consequence. • The risk of neutropenia is significant both from underlying CLL and from treatment with venetoclax. The neutropenia is usually manageable with standard of care treatments including antibiotics and G-CSF. Importantly, no correlation was found between rates of neutropenia and infections. • Drug-drug interactions were seen with CYP3A inducers and inhibitors and P-gp inhibitors. • Venetoclax is metabolized by the liver, and a very limited number of patients with moderate hepatic impairment were treated with venetoclax. • Although venetoclax is not excreted by the kidney, and there was no difference in exposure in patients with renal impairment, there is an increased risk of TLS in patients with renal impairment. 	<p>All safety information to date has been from single-arm trials, so contribution of the underlying disease is difficult to determine. However, no major safety concerns were identified except for the on-target events of TLS and neutropenia. The confirmatory trial for venetoclax will be a randomized trial which will allow isolation of the contribution of venetoclax to the adverse reactions. A dedicated study of venetoclax in patients with hepatic impairment will be required to identify the safe dose and specific risks in that patient population.</p> <p>Despite the known safety concerns, the risks are acceptable in patients with relapsed or refractory CLL who harbor the 17p deletion and require treatment for their disease.</p>
<p>Risk Management</p>	<ul style="list-style-type: none"> • The risk of TLS is managed through ramp up dosing of venetoclax, risk assessment, and prophylaxis based on risk level. • Ramp up dosing for venetoclax is managed through a Start Pack which provides the first 4 weeks of dosing (20 mg, 50 mg, 100 mg, and 200 mg) in blister packs of 7 doses at each level. The final target dose of 400 mg is supplied in bottles containing 100 mg tablets. • Risk assessment is based on baseline lymph node size and absolute lymphocyte count. Prophylaxis for TLS is provided through strict hydration guidelines (oral for low risk and oral with intravenous for medium- and high-risk patients), anti-hyperuricemics, close laboratory monitoring, and hospitalization if indicated. • Venetoclax is contraindicated with strong CYP3A inhibitors. Moderate CYP3A inhibitors, 	<p>Labeling (including a Medication Guide and Quick Start Guide with the Start Pack) is adequate to address the safety issues associated with venetoclax.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>strong and moderate CYP3A inducers, P-gp inhibitors, and P-gp substrates with a narrow therapeutic index should be avoided or the dose of venetoclax should be adjusted appropriately.</p> <ul style="list-style-type: none">• Venetoclax should be taken with food which increases the bioavailability.	

2. Background

On October 29, 2015 AbbVie Inc. submitted a New Drug Application (NDA) for venetoclax, a small molecule inhibitor of BCL-2. Approval of this application would be for the first inhibitor of BCL-2. BCL-2 is important because resistance to apoptosis is a major mechanism of the development of malignancy. BCL-2 is overexpressed in some lymphoid malignancies and is associated with increased resistance to chemotherapy. CLL cells are almost universally dependent on BCL-2; therefore, inhibition of BCL-2 can restore apoptosis in CLL cells.

In vitro studies showed that venetoclax binds with high affinity to BCL-2. Venetoclax did not cause inhibition of cell lines that were not dependent on BCL-2 family members. In a BCL-2 dependent cell line, venetoclax rapidly induced apoptosis. In cell lines with 17p deletion, venetoclax was also potent.

Breakthrough Therapy designation was granted on April 27, 2015 to venetoclax for the treatment of patients with relapsed/refractory CLL who harbor the 17p deletion cytogenetic abnormality. The only other application approved to treat patients with CLL 17 p deletion is ibrutinib.

This application was given priority review. Venetoclax is not approved in any country at this time.

3. Product Quality

There are no issues that would preclude approval from a CMC perspective. The product presentation is film-coated tablets containing 10, 50, or 100 mg of venetoclax per tablet with the following excipients: copovidone, polysorbate 80, colloidal silicon dioxide, anhydrous dibasic calcium phosphate, and sodium stearyl fumarate. The expiration-dating period of 24 months is granted for the drug product packaged in either bottles or blisters and stored at or below 30°C. The facilities inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. Venetoclax is a selective and orally bioavailable small molecule inhibitor of the B-cell lymphocyte-2 (Bcl-2) anti-apoptotic protein.

The pharmacology and toxicology studies reviewed included pharmacodynamics, safety pharmacology, genotoxicity, repeat dose toxicity, and reproductive and developmental toxicity. *In vitro*, venetoclax is cytotoxic to cells overexpressing Bcl-2. Pharmacology studies indicate venetoclax-mediated apoptosis involves binding to Bcl-2, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. Venetoclax was shown to have antitumor activity *in vivo* in a human acute lymphocytic leukemia xenograft (mouse) model. Additionally, lymphocyte decreases were observed in the toxicology studies, which is an expected effect of Bcl-2 inhibition.

The potential for adverse venetoclax-mediated effects on the central nervous system and respiratory systems was evaluated in rodents, and cardiovascular safety pharmacology endpoints were as evaluated in an in vitro hERG assay and in vivo in dogs. Venetoclax has an acceptable safety pharmacology profile at doses achieving plasma concentrations relevant to the recommended human daily dose of 400 mg. Repeat dose general toxicology studies (26-week mouse and 39-week dog) indicate that venetoclax primarily affects the hematologic system (decreased lymphocytes and red blood cell mass), and the male dog reproductive system (testicular germ cell depletion in dogs).

Based on the findings in animals, Venclaxta may compromise male fertility and cause fetal harm. Fertility and early embryonic development studies in male and female mice revealed no effects of venetoclax on estrus cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at doses up to 600 mg/kg/day, which is approximately 2.8 and 3.2 times the human exposure at 400 mg (based on AUC) in male and female mice, respectively. No teratogenicity was observed in either the mouse or the rabbit embryofetal development studies. Venetoclax was fetotoxic in mice at 150 mg/kg/day (a dose yielding exposures approximately 1.2 times the human exposure at 400 mg (based on AUC), and was also associated with post-implantation loss and decreased fetal body weights. In rabbits, venetoclax produced maternal toxicity at 300 mg/kg/day, but no fetal toxicity (300 mg/kg/day approximates 0.2 times the human exposure at 400 mg (based on AUC)). The label will state that woman should discontinue breastfeeding while taking Venclaxta.

No carcinogenicity studies have been conducted with venetoclax. Venetoclax was not mutagenic in a bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an in vitro assay using human peripheral blood lymphocytes, and was not clastogenic in an in vivo mouse bone marrow micronucleus assay.

5. Clinical Pharmacology

The selected dose and dosing regimen is supported by exposure-response analyses based on pooled data from the pivotal Phase 2 trial and a key dose-finding Phase 1 trial. ORR appears to plateau at doses greater than 400 mg. The relationship between exposure and safety (grade 3/4 neutropenia and infection) is relatively flat and supports the selection of proposed dosing regimen.

After oral administration, venetoclax is metabolized by the liver and entirely excreted by the fecal route. Dose adjustment for patients with mild and moderate renal or hepatic impairment is not recommended based on population PK analyses; however, such patients should be closely monitored for toxicity during initiation and dose ramp-up phases due to a trend of increased adverse events in these patients.

Venetoclax is substrate of CYP3A4/5 and P-gp and inhibitor of P-gp. Concomitant use of strong CYP3A inhibitors should be avoided during dose ramp-up phase. For patients on stable dose of venetoclax who require treatment with concomitant moderate or strong CYP3A inhibitors, the dose of venetoclax should be reduced 2- and 4-fold, respectively. Concomitant use of strong and moderate inducers of CYP3A, P-gp inhibitors and narrow therapeutic index P-gp substrates should also be avoided.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical- Efficacy

This application is supported by the results of a phase 2, single-arm trial of venetoclax for the treatment of patients with CLL harboring the 17p deletion who had received at least one prior therapy. The major efficacy outcome measure was ORR according to the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response as evaluated by an independent review committee (IRC). Duration of response (DOR) was an additional outcome measure.

The trial enrolled 106 patients who had received at least one prior therapy with 17p deletion, as detected by an FDA-approved CLL fluorescence in situ hybridization (FISH) probe kit. Patients had a median of 2.5 prior treatments (range 1-10). The ORR by IRC was 80% (95% CI: 71%, 87%) with 8% complete remission (including 2% complete remission with incomplete marrow recovery). Minimal residual disease (MRD) was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with venetoclax. Three percent of the patients in the intent-to-treat population achieved a complete remission (CR or CRi) and were also negative for MRD in the bone marrow and peripheral blood. The median time to first response was 0.8 months (range: 0.1 to 8.1 months). Median DOR has not been reached with approximately 12 months median follow-up. The DOR ranged from 2.9 to more than 19 months.

8. Safety

Safety data were evaluated in 240 patients with previously-treated CLL who were treated with single-agent venetoclax at a target dose of 400 mg orally daily. The most common (greater than or equal to 20%) adverse reactions of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Serious adverse reactions were reported in 44% of patients, and the most common (greater than or equal to 2%) serious adverse reactions were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia, anemia, and TLS.

Due to a rapid reduction in tumor volume, TLS is an important identified risk when initiating venetoclax. The risk of TLS is reduced with stratification by tumor burden, prophylaxis with hydration and anti-hyperuricemics, frequent blood chemistry monitoring and correction of electrolyte abnormalities. In patients with higher risk features, hospitalization for IV hydration, electrolyte monitoring, and aggressive correction of electrolyte abnormalities may be required. In 66 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6% with no clinical events. All events were laboratory TLS and occurred in patients who had a lymph node(s) greater than or equal to 5 cm or ALC greater than or equal to 25 x 10⁹/L.

9. Advisory Committee Meeting

Venetoclax was not referred to the Oncology Drug Advisory Committee because there were no clinical efficacy and safety issues that would benefit from ODAC discussion.

10. Pediatrics

The Applicant was granted Orphan Drug Designation for venetoclax for the treatment of patients with CLL and therefore is exempt from pediatric studies under the Pediatric Research Equity Act (PREA).

11. Postmarketing Recommendations

- Risk Evaluation and Management Strategies (REMS)

Safety issues with venetoclax can be effectively communicated through labeling and the MedGuide. A REMS is not required.

- Postmarketing Requirements (PMRs) and Commitments (PMCs)

See action letter.

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

/s/

TAMY E KIM
04/11/2016

RICHARD PAZDUR
04/11/2016