CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208573
Applicant	AbbVie, Inc.
Date of Submission	October 29, 2015
PDUFA Goal Date	June 29, 2016
Proprietary Name / **Non-Proprietary Name**	Venclexta/venetoclax
Dosage Form(s) / Strength(s)	Tablets: 10 mg, 50 mg, 100 mg
Applicant Proposed Indication(s)/Population(s)	Patients with relapsed or refractory chronic lymphocytic leukemia who have received at least one prior therapy, including those with 17p deletion
Action/Recommended Action for NME:	Accelerated Approval
Approved/Recommended Indication/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

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lori Ehrlich, M.D., Ph.D. /Virginia Kwitkowski, BSN, MS, ACNP-BC
Regulatory Health Project manager	Beatrice Kallungal, BS, MS
Statistical Review	Qing Xu, Ph.D./Yuan-Li Shen, Dr. Ph.
Pharmacology Toxicology Review	Ramadevi Gudi, Ph.D./ Emily Place, Ph.D./Christopher

	Sheth, Ph.D./John Leighton, Ph.D.
OPQ Review	Rajiv Agarwal/Monica Cooper/Gerlie Gieser/Ruth Moore /Tracey Rogers, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Guoxiang Shen, Ph.D./Lian Ma, Ph.D./Justin Earp, Ph.D./Sarah Dorff, Ph.D./Bahru Habtemariam, Pharm.D./Nitin Mehrotra, Ph.D./Rosane Charlab Orbach, Ph.D./Nam Atiqur Rahman, Ph.D.
OPDP/DMPP/DMEPA	Nisha Patel, Pharm.D./ Rowell Medina, Pharm.D. / Sharon R. Mills, BSN, RN, CCRP/ LaShawn Griffiths, MSHS-PH, BSN, RN/Kathleen Davis
OSI	Anthony Orencia M.D., F.A.C.P., Janice Pohlman M.D., M.P.H.
CDTL Review	Virginia Kwitkowski, BSN, MS, ACNP-BC
OSE/DEPI	none
OSE/DMEPA/OMP/OPDP	Kevin Wright/Nicole Garrison, Pharm.D., BCPS/Yelena Maslov, Pharm.D./Merchant, Pharm.D., MS/Nisha Patel/Kathleen Davis
OSE/DRISK	Mona Patel, Pharm.D./Naomi Redd, Pharm.D./Cynthia LaCivita, Pharm.D.
Other	Dinko Rekic/Jiang Liu/Huifang Chen/Qianyu Dang/Michael Li/ Norman L Stockbridge, M.D. Rowell Medina, Pharm.D./Sharon R. Mills, BSN,RN,CCRP/LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

APPEARS THIS WAY ON ORIGINAL

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Relapsed or refractory CLL is a serious and life-threatening disease with approximately 15,000 new cases per year, primarily in the elderly. CLL has several identified prognostic factors. The 17p gene deletion has been identified as a very poor prognostic factor with survival duration generally less than 24 months. Several therapies are FDA-approved for the treatment of R/R CLL including combination therapy (fludarabine, cyclophosphamide, rituximab), ibrutinib, idelalisib with rituximab, ofatumumab, and chlorambucil. However, the only FDA-approved therapy for patients with 17p deletion is ibrutinib which has an overall response rate of 48% in this disease. CLL remains incurable except for allogeneic stem cell transplantation.

The Applicant is developing venetoclax, an oral, small molecule inhibitor of BCL-2 (B cell lymphoma protein 2), for the treatment of relapsed or refractory chronic lymphocytic leukemia (R/R CLL), including those patients whose disease harbors the 17p gene deletion. The Applicant submitted data from two single arm trials evaluating the treatment effect. M13-982 was a phase 2, single-arm trial, M13-982, enrolling patients with relapsed or refractory CLL harboring the 17p deletion. M12-175 was a single arm phase 1 dose finding study enrolling patients with relapsed or refractory CLL after one prior therapy. The Applicant submitted this application for accelerated approval and thus the application is subject to 21 CFR 312.500 provisions which require the submitted data for each indication to be better than available therapy.

The overall response rate in M13-982 was 80.2% with a complete response rate of 7.5%. Given the FDA-reviewed ibrutinib data with a lower response rate and no complete responses, these M13-982 data suggest that venetoclax is better than available therapy. (b) (4)

The safety profile is characterized through three single-arm trials of single agent venetoclax for the treatment of patients with R/R CLL and supported by safety information from venetoclax in combination with other therapy and for the treatment of other cancers. The main safety concerns are the risk of tumor lysis syndrome and neutropenia. The risk of tumor lysis syndrome is mitigated through the use of venetoclax ramp-up dosing over 5 weeks, risk stratification based on tumor burden, and prophylaxis measures with hydration, anti-hyperuricemics, laboratory monitoring, and potential hospitalizations.

The risks are communicated through the Prescribing Information including a Medication Guide, a Start Pack for dosing during the first 4 weeks of the ramp up period, and a Quick Start Guide provided with the Start Pack. Potential drug-drug interactions are identified in the prescribing information.

Venetoclax is the first in class novel oral therapeutic agent for the treatment of patients with relapsed or refractory CLL with 17 p deletion. The efficacy of venetoclax for the treatment of patients with R/R CLL with the 17p deletion is supported based on a surrogate endpoint of overall response rate. The safety in patients with R/R CLL is acceptable with management of the risk of tumor lysis syndrome which are addressed through appropriate labeling. Venetoclax is an important addition to the treatment armamentarium for patients with R/R CLL with 17p deletion.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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, predominately 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 CLL with 17p del is generally less than 24 months.	Relapsed or refractory CLL with 17p deletion is serious, life threatening, and rare in frequency. The median duration of survival for patients with 17p del is poor. Relapsed or refractory CLL generally affects the elderly.
Current Treatment Options	• 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	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CLL include combination chemo-immunotherapy (fludarabine, cyclophosphamide, rituximab), ibrutinib, idelalisib with rituximab, ofatumumab and chlorambucil. • The response rates to standard therapies for patients with CLL with17p del are significantly lower. • The only FDA-approved therapy for the treatment of patients with 17p deleted CLL is ibrutinib.	several new approvals for relapsed or refractory CLL, the disease remains incurable for most patients, and as such is an unmet medical need. The response rates in patients whose disease has the 17p deletion are lower and the available therapies are much more limited. Additional therapies with differing mechanisms of action and adverse event profiles are needed.
Benefit	• 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 overall response rate 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 overall response rate in 106 patients with CLL 17p del 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 phase 2 trial in patients with relapsed or refractory CLL with 17p deletion met the primary endpoint of overall response rate. 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. Overall response rate is considered a surrogate endpoint for progression-free or overall survival in CLL. Therefore, venetoclax is recommended for accelerated approval for patients with 17p del. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the target dose of 400 mg daily. (b) (4)	(b) (4)
Risk	• 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.	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 tumor lysis syndrome 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 specific risks in that patient population. 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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 tumor lysis syndrome in patients with renal impairment.	
Risk Management	• The risk of tumor lysis syndrome 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 tumor lysis syndrome 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, 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. • Venetoclax should be taken with food which increases the bioavailability. Labeling – includes a complete description of	Labeling (including a Medication Guide and Quick Start Guide with the Start Pack) is adequate to address the safety issues associated with venetoclax.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the safety observed in the trial along with focused description in certain highlighted areas.	

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 the approval of 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

No issues were identified that would preclude approval. 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 30ºC.

The facilities inspection is acceptable.

I concur with the recommendation for approval.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the secondary review:

Venetoclax is a selective and orally bioavailable small molecule inhibitor of the B-cell lymphocyte-2 (Bcl-2) anti-apoptotic protein, being developed for the above indication. Venclexta tablets will be initially taken at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. The Established Pharmacological Class of "Bcl-2 inhibitor" was determined to be both scientifically valid and clinically meaningful.

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 (a hallmark of various hematologic malignancies). 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, Venclexta 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 Venclexta.

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.

I concur with the recommendation for approval.

5. Clinical Pharmacology

No issues that would preclude approval were identified. The following text is from the primary review:

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.

The review team requested the following PMRs:

The applicant is required to conduct the following post-marketing requirement trials:
1. Conduct a pharmacokinetic trial to determine the appropriate dose of venetoclax in patients with varying degree of hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf . Submit the final study report as PMR under the NDA.

2. Conduct a pharmacokinetic trial to evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp to determine dose recommendations for co-administration of narrow therapeutic index P-gp substrates with venetoclax in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf . Submit the final study report as PMR under the NDA.

I concur with the Clinical Pharmacology review and the request for PMRs.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The Applicant provided data for venetoclax, an oral, small molecule inhibitor of BCL-2 (B cell lymphoma protein 2), for the treatment of relapsed or refractory chronic lymphocytic leukemia (R/R CLL), including those patients whose disease harbors the 17p gene deletion. Clinical efficacy data from two trials was submitted: M13-982 and M12-175. M13-982 was a phase 2, single-arm trial, M13-982, enrolling patients with relapsed or refractory CLL harboring the 17p deletion. M12-175 was a single arm phase 1 dose finding study enrolling patients with relapsed or refractory CLL after one prior therapy. The Applicant submitted this application for accelerated approval and thus the application is subject to 21 CFR 312.500 provisions which require the submitted data for each indication to be better than available therapy.

Both trials enrolled the appropriate patient populations (CLL with prior treatment) as outlined in their protocol. All patients received at least one prior therapy. The overall response rate in M13-982 was 80.2% with a complete response rate of 7.5%. Given the FDA-reviewed ibrutinib data with a lower response rate and no complete responses, these M13-982 data suggest that venetoclax is better than available therapy. (b) (4)

I concur with the findings of the clinical and statistical review teams regarding the recommendations for approval. The Applicant has provided sufficient evidence to grant accelerated approval for venetoclax for the treatment of patients with CLL associated with deletion 17p who have received one prior therapy. (b) (4)

8. Safety

The safety profile was characterized through three single-arm trials of single agent venetoclax for the treatment of patients with R/R CLL and supported by safety information from venetoclax in combination with other therapy and for the treatment of other cancers. All data was pooled for the analyses. The main safety concerns are the risk of tumor lysis syndrome (TLS) and neutropenia. The risk of tumor lysis syndrome is mitigated through the use of venetoclax ramp-up dosing over 5 weeks, risk stratification based on tumor burden, and prophylaxis measures with hydration, anti-

hyperuricemics, laboratory monitoring, and potential hospitalizations. These mitigation measures should ensure the safe use of this product.

The most common adverse reactions (≥20%) were neutropenia, diarrhea, nausea, upper respiratory tract infection, and fatigue. The most common serious adverse reactions were: pneumonia, febrile neutropenia and TLS. The most frequent causes of discontinuation were diarrhea, nausea, and increased blood creatinine.

The majority of the on-study deaths were due to disease progression. No predictable pattern was observed. From the review:

There were single events of death due to AE from the following causes: hemorrhagic stroke, hepatic function abnormal, septic shock, cardiopulmonary failure, sudden death, small intestine obstruction, pneumonia viral, and death (NOS). All deaths were considered "not related" or "probably not related" to study drug by the investigator, except for the single event of "sudden death". This patient experienced fatal tumor lysis syndrome after escalating to 1200 mg. The other causes of death are consistent with an elderly CLL patient population with frequent comorbidities.

I concur with the reviewers. The safety data collected is adequate for labeling with respect to warnings and precautions. Prescribers must adhere to the warnings particularly with respect to Tumor Lysis Syndrome. Routine Pharmacovigilance should be adequate for post-approval safety monitoring.

9. Advisory Committee Meeting

This application was not referred for an Advisory Committee meeting as no clinical efficacy or safety issues arose that required an Advisory Committee meeting and discussion.

10. Pediatrics

N/A- Orphan Designation

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) did not find the data unreliable in support of the application.

Financial Disclosure information was provided and reviewed. From the secondary review:

Four investigators and two sub-investigators were identified to have financial disclosures; one disclosure was for proprietary or financial interest in the product tested in the clinical study, and five disclosures were for significant payments having total value in excess of $25,000 from AbbVie or Genentech/Roche. The sites enrolled

(b) (6) *and* (b) (6) *subjects. With the small number of patients enrolled at any site, the enrollment of patients by these investigators is not expected to bias the outcome of the study results. Removal of the* (b) (6) *patients enrolled at these sites from the main cohort analysis resulted in a similar o erall response rate.*

The results of trial M13-982 are not likely to be due to bias associated with financial gain.

12. Labeling

All disciplines made recommendations for labeling.

Indication granted as discussion in Section 7

No boxed warning

Warnings and Precautions subsections encompass:

1) Tumor Lysis Syndrome with recommendation for prevention including hospitalization (if patient high risk as was done in the submitted studies) hydration, agents to prevent hyperuricemia, and ramped up treatment schedule for venetoclax
2) Neutropenia
3) Immunization with live vaccines
4) Embryo-fetal Toxicities

I agree with the proposed labeling and at the current time do not have any additional suggestions.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

The label gives sufficient guidance for management. The recommendations in the labeling particularly for tumor lysis syndrome risk management were used in the trials.

- Other Postmarketing Requirements and Commitments

Subpart H-- Clinical

Venetoclax is recommended for approval under Subpart H (the accelerated approval provisions). The approval is subject to a Postmarketing Requirement to verify and describe the clinical benefit of venetoclax.

PMR#1- Submit the complete final report and data from trial GO28667, a randomized, phase 3 trial comparing venetoclax and rituximab with bendamustine and rituximab in patients with relapsed or refractory CLL, including CLL with deletion 17p

Clinical Pharmacology
The Clinical Pharmacology review team has recommended the following post-marketing requirements to enable complete dosing information for patients with hepatic impairment and to further evaluate drug-drug interactions:

PMR #2 Description: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of venetoclax compared to subjects with normal hepatic function. Submit a complete final study report with all supporting datasets for trial M15-342 entitled, “A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment”.

PMR # 3 Description: Evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final study report with all supporting datasets.

Refer to action letter for final wording and milestones of the post-marketing requirements.

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

/s/

ANN T FARRELL
04/08/2016