CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s013

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 29, 2019

To: Beatrice Kallungal, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nazia Fatima, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for VENCLEXTA® (venetoclax) tablets, for oral use

NDA: 208573/S-013

Office of Prescription Drug Promotion (OPDP) has reviewed the proposed product labeling (PI) and Medication Guide (MG) for VENCLEXTA® (venetoclax) tablets, for oral use (Venclexta). As requested by Division of Hematology Products (DHP) consult dated February 21, 2019.

OPDP's comments on the proposed labeling are based on the draft PI and draft MG send to OPDP on April 23, 2019. OPDP has reviewed the draft PI and has no comments. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

NAZIA FATIMA
04/29/2019 10:30:14 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 26, 2019
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	VENCLEXTA (venetoclax tablets), for oral use
Application Type/Number:	NDA 208573
Supplement Number:	S-013
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On February 6, 2019, AbbVie, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 208573/S-013 for VENCLEXTA (venetoclax tablets), for oral use. With this supplement, the Applicant provides the Agency with the Real Time Oncology Review (RTOR) early package submission for Venetoclax in Combination with Obinutuzumab in Previously Untreated Patients with Chronic Lymphocytic Leukemia (1L CLL) based on pivotal phase 3 study B025323/CLL14 and phase 1b supporting study GP28331.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on Feb 24, 2019, and February 21, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VENCLEXTA (venetoclax tablets).

2 MATERIAL REVIEWED

- Draft VENCLEXTA (venetoclax tablets) MG received on February 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 23, 2019.
- Draft VENCLEXTA (venetoclax tablets) Prescribing Information (PI) received on February 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 23, 2019.
- Approved VENCLEXTA (venetoclax tablets) labeling dated November 21, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSAN W REDWOOD
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SHAWNA L HUTCHINS
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U.S. FOOD & DRUG ADMINISTRATION

Consult Memorandum

Date:	April 26, 2019
To:	Nicholas Richardson (MO) and Rosa Lee-Alonzo (RPM) CDER/OND/OHOP/DHP
From:	Aaron Schetter CDRH/OIR/DMGP
Through:	Donna Roscoe and Reena Philip
Subject:	NDA208573S013; Venetoclax in Combination with obinutuzumab in Previously Untreated Patients with Chronic Lymphocytic Leukemia (1L CLL)
Drug Name:	VENCLEXTA
Drug Sponsor	Roche Genentech and AbbVie, Inc
Biomarker(s):	MRD by ASO-PCR for use additional efficacy data
Device Name:	ASO-PCR
CDRH Tracking Number:	ICC1900229
Related Submissions:	(b) (4) IND110159 (multiple consults), NDA208573/S007 (ICC1800216)

Aaron J. Schetter -S
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I. BACKGROUND and PURPOSE

In this NDA supplement, the sponsor provides data to support a new indication for Venetoclax in Combination with obinutuzumab in Previously Untreated Patients with Chronic Lymphocytic Leukemia (1L CLL) based upon pivotal phase 3 study BO25323/CLL14 and phase 1b supporting study GP28331.

The sponsor proposes to include MRD data into drug label. CDRH has been consulted to comment on the acceptability of the assay used to generate the MRD data. CDRH has provided extensive reviews of the ASO-PCR assay under (b) (4) IND110159 and NDA208573/S007. Previously, CDRH has reviewed the ASO-PCR assay as run by the (b) (4) and found it analytically acceptable.

It was noted in IND110159 (ICC190014) that the sponsor made minor changes to the ASO-PCR test used in the trial. The change of interest is the change to the Albumin control. CDRH offered the following comment in January, 2019.

> The (b) (4) has added a lower dilution of Albumin DNA (1500 copies) to the standard curve. We understand the general use of Albumin control to verify that ~90,000 copies of Albumin are detected in 600 ng DNA. This verifies that ~90,000 cells are being evaluated by the MRD assay. Acceptance criteria is 75%-125% of 90,000 and if samples are out of this range, DNA is re-extracted. If the re-extracted sample fails, you may normalize to Albumin, in some cases. You appear to be using the lower dilution of Albumin (1500 copies) to allow MRD measurements on samples when < 7,500 cells are being evaluated. It is problematic to call any sample in this range as MRD(-) since there would not be enough cells evaluated to have confidence in the res ult. Please clarify what is the minimum Albumin copy number

that is allowable for MRD(-) calculations. In addition, provide a data column for albumin copy number in the SDTM and ADAM datasets for the MRD data from the CLL14 trial.

The sponsor has provided a response in the current NDA supplement.

CDRH has been asked to provide comments about the data that was submitted. Specifically, this review will focus on 6 patient results that were affected by the change of allowing MRD (-) calls when Albumin is below 67500 copies (75% of the expected 90,000 copies).

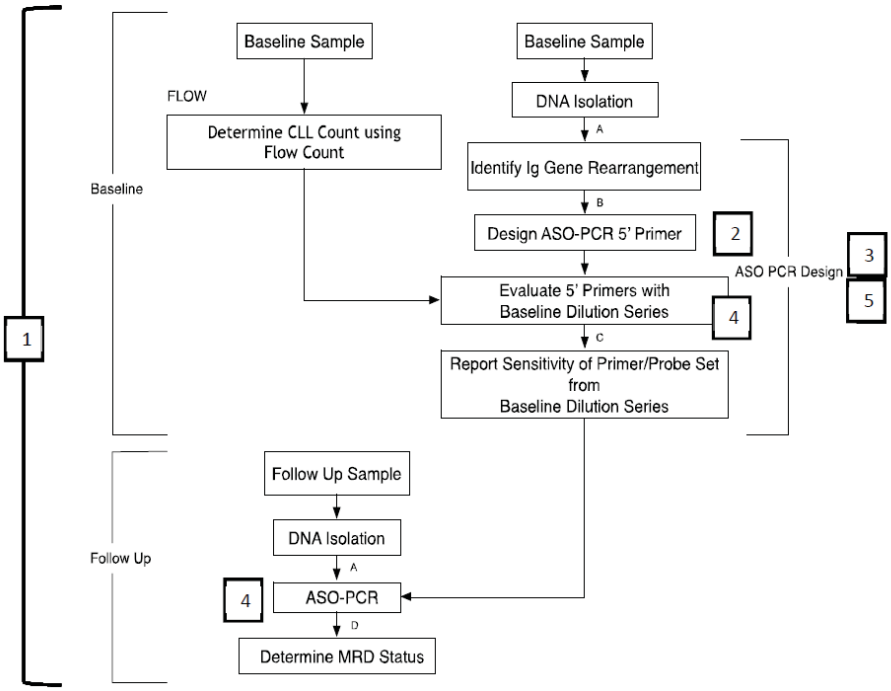
II. Regulatory History Venetoclax

In the United States, the original NDA (208573) for VENCLEXTA® (venetoclax tablets), designated as breakthrough therapy on 27 April 2015, was granted accelerated approval on 11 April 2016 for the treatment of patients with CLL with del(17p), as detected by an FDA-approved test, who had received at least 1 prior therapy. In addition, the Sponsors submitted three supplemental NDAs; one for a labeling update for drug-drug interactions (NDA 208573/S-003; Reference ID: 4198479), which was approved on 20 December 2017, and two for the additional indication in R/R CLL (NDA 208573/S-004 and NDA 208573/S-005), both of which were approved on 8 June 2018 (Reference ID: 4275193). S-004 contributed to the full approval of venetoclax for the treatment of patients with CLL or SLL, with or without del(17p), who received at least 1 prior therapy. Furthermore, on 7 September 2018, the FDA approved the inclusion of MRD data from the pivotal Phase 3 Study GO28667/MURANO in the clinical section of the U.S Package Insert (USPI) under the labeling supplement NDA 208573/S-007 (Reference ID: 4316460).

III. DEVICE USE IN THE TRIAL

ASO-PCR MRD assay as run by the (b) (4).

ASO-PCR Workflow



Basic Protocol for ASO-PCR measurement:

- **DNA is isolated**
- **Nanodrop is used to measure DNA concentration**
- **600 ng DNA is the input and assumed to be 90,000 cells.**
- **Run on Roche LC480**
- **MRD-result compared to dilution series to estimate MRD level**
- **Albumin is the PCR control, expect 90,000 copies. Acceptance criteria is 75%-125% of 90,000. If samples are out of this range, DNA is re-extracted. If the re-extracted sample fails, they may normalize to albumin.**

MRD Cutoff is 10-4, or 1/10,000 cells

IV. Information from sponsor

Based on the interactions between the Agency and the sponsor, the sponsor submitted "INFORMATION REQUEST: CLL14 (BO25323) ALBUMIN COPY NUMBER DATA AND ANALYSIS OF THE SCOPE AND IMPACT OF LOW ALBUMIN COPY NUMBER ON CLL14 MRD RESULTS"

The sponsor indicated that the assay would provide a result if Albumin counts ≥10,000

Table 1 Dilution Series of the Baseline Sample and Correlation to Tumor Load and DNA Target Copies

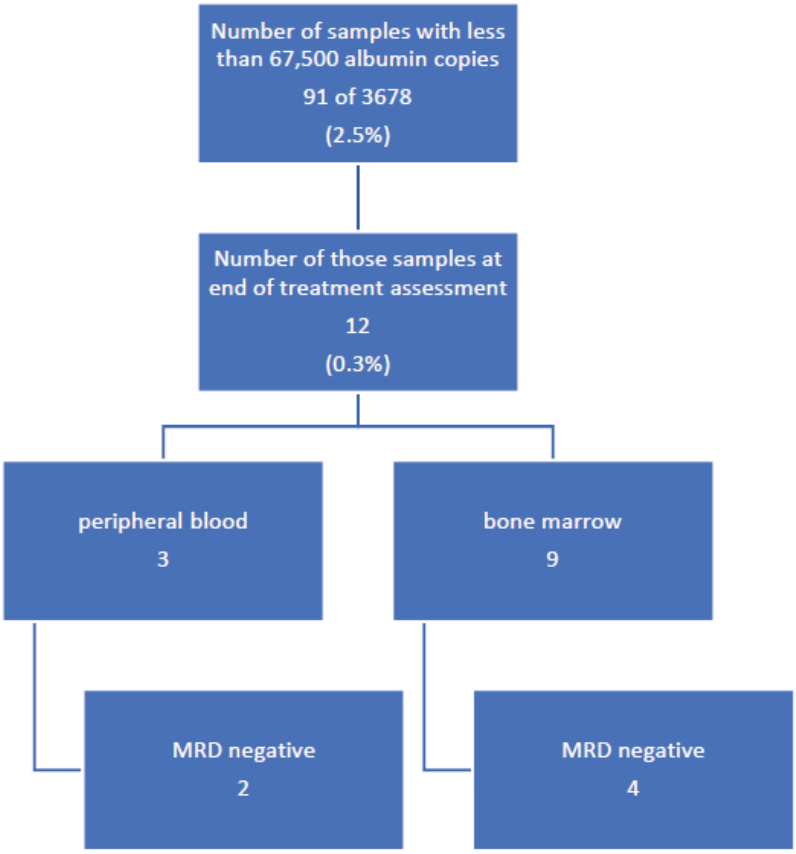
Threshold	1×10^{-4}		
Tumor load (%)	0.01		
Total albumin copies CLL and normal (cell equivalent)	90000	67500	10000
CLL DNA target copies (cell equivalent)	9	6.5	1

The sponsor provided the MRD information from the trial to indicate how often Albumin levels were below 67,500.

b) Impact of Albumin on EOT samples

Among the 91 samples with albumin < 67,500 copies, 12 of these were at EOT assessment, of which 3 were derived from PB and 9 were BM samples; 2 of the PB and 4 of the BM were determined as MRD-negative by ASO-PCR (Figure 1).

Figure 1 Impact of Albumin on EOT Samples



Reviewer Note: This indicates that there are a total of 6 results (2 PB, 4 BM) that were impacted by using Albumin < 67,500.

The sponsor provided a sensitivity analysis in which all 6 results were changed from MRD(-) to MRD(+). This is the most conservative way of handling; i.e, concluding worst case scenario by determining that if a sample did not have enough DNA evaluated, it would automatically be MRD(+).

Table 2 Sensitivity Analyses of Key MRD Secondary Endpoints

	MRD Reported in CSR[c]		Sensitivity Analysis[d]	
Parameter[a]	**GCIb (N = 216)**	**VEN + G (N = 216)**	**GCIb (N = 216)**	**VEN + G (N = 216)**
MRD-Negativity Rate[b]-Peripheral Blood at EOT Assessment				
MRD negative (at 10^{-4})	76 (35.2%)	163 (75.5%)	75 (34.7%)	162 (75.0%)
95% CI	[28.83, 41.95]	[69.17, 81.05]	[28.39, 41.48]	[68.67, 80.63]
Difference in MRD negative rates [95% CI]	40.28 [31.45, 49.10]		40.82 [31.44, 49.11]	
P-value (CMH test)	p < 0.0001		p < 0.0001	
MRD-Negativity Rate[b]–Bone Marrow at EOT Assessment				
MRD negative (at 10^{-4})	37 (17.1%)	123 (56.9%)	35 (16.2%)	121 (56.0%)
95% CI	[12.36, 22.83]	[50.05, 63.64]	[11.55, 21.81]	[49.12, 62.75]
Difference in MRD negative rates [95% CI]	39.81 [31.27, 48.36]		39.81 [31.32, 48.31]	
P-value (CMH test)	p < 0.0001		p < 0.0001	
MRD-Negativity Rate[b] in CR Patients–Peripheral Blood (Investigator Assessment) at EOT Assessment				
MRD negative (at 10^{-4})	31 (14.4%)	91 (42.1%)	31 (14.4%)	91 (42.1%)
95% CI	[9.96, 19.75]	[35.46, 49.02]	[9.96, 19.75]	[35.46, 49.02]
Difference in MRD negative rates [95% CI]	27.78 [19.45, 36.10]		27.78 [19.45, 36.10]	
P-vale (CMH test)	p < 0.0001		p < 0.0001	
MRD-Negativity Rate[b] in CR Patients–Bone Marrow (Investigator Assessment) at EOT Assessment				
MRD negative (at 10^{-4})	23 (10.6%)	73 (33.8%)	22 (10.2%)	73 (33.8%)
95% CI	[6.87, 15.55]	[27.52, 40.53]	[6.49, 15.01]	[27.52, 40.53]
Difference in MRD negative Rates [95% CI]	23.15 [15.37, 30.93]		23.61 [15.87, 31.35]	
P-vale (CMH test)	p<0.0001		p<0.0001	

CMH = Cochran-Mantel-Haenszel; CR = complete response; EOT = end of treatment (i.e., 3 months after treatment completion/early termination); GCIb = obinutuzumab + chlorambucil; MRD = minimum residual disease; VEN + G = venetoclax+obinutuzumab.

a. The overall type-1 error rate at a pre-specified 2-sided level alpha = 0.05 was controlled for all endpoints in this table.
b. By ASO-PCR.
c. Source: Study BO25323 CSR Table 19.
d. Source: t_ef_mrdsens_EOTBLPCR_NSFRFL_323_IT; t_ef_mrdsens_EOTBMPCR_NSFRFL_323_IT; t_ef_mr4sens_EOTBLPCR_NSFRFL_323_IT; t_ef_mr4sens_EOTBMPCR_NSFRFL_323_IT.

Reviewer Note: There are no major differences in conclusions. For Blood, 2 values changed. One was in the GCLb arm and one was in the VEN+G arm. For Bone marrow, 4 values changed, 2 in the GCLb arm and 2 in the VEN+G arm. This did not affect the original conclusion (compare MRD rates in CSR numbers versus MRD in the "Sensitivity Analysis").

The sponsor provided information on the 6 MRD negative test results that had Albumin counts less than 10,000. The sponsor also tested a subset of samples with an NGS-based MRD test. That test reported number of cells evaluated and MRD status. When available, the sponsor provided all the information for both tests.

The 6 results were from the "FOLLOW-UP Month 3" timepoint at the end of treatment, which is the single timepoint used for MRD status for efficacy. The sponsor also collected MRD data at other timepoints throughout the study. This is why figure 1 contains 91 of 3678 MRD assessment had < 67500 copies of Albumin. Of these 91, 20 were MRD(-) by ASO-PCR and were tested by the NGS-assay. Albumin counts ranged from 30800 to 65600. All 20 MRD(-) results were confirmed as MRD(-) from the NGS assay. Therefore, one can be more confident in MRD(-) results if Albumin levels are above 30,000.

The 6 results in question were:

Blood/PB	Patient ID	Albumin	MRD by ASO-PCR	MRD by NGS
BM	(b) (6)	64900	Negative	N/A
BM		59200	Negative	N/A
BM		16600	Negative	N/A
Blood		41700	Negative	Negative
BM		55100	Negative	N/A
Blood		56500	Negative	Negative

Note: 2 of 6 samples were tested by an NGS assay and both were confirmed MRD(-). 5 of 6 samples have Albumin counts > 40,000. Based on the data the sponsor has provided, one can be confident that all 5 are MRD(-) (100% of 20 samples that were MRD(-) by ASO-PCR with less than 67,500 Albumin copies, were also MRD(-) by the NGS assay).

Sample ID (b) (6) only had 16600 Albumin counts. There is less confidence in the analytical validity of this result. If this patient sample were a low positive (i.e. MRD level at 2 X 10-4) it may have been missed. However, this single result would not be expected to have an overall impact on the final conclusions.

V. CDRH RESPONSE TO CDER

CDRH has previously reviewed the analytical validity of the ASO-PCR test and found it acceptable. The analytical validity studies were based on samples with Albumin levels within 75%-125% of the target Alubumin level of 90,000 (67,500 to 111,250).

In BO25323, there are 6 total MRD results that could be impacted by allowing MRD negative calls on samples with DNA < 67,500. Five (5) of the sample results can confidently be called MRD(-) and there is no objection to including them as MRD(-). Patient Sample ID (b) (6) may not be a reliable MRD (-) result as only 16,600 Albumin counts were present. It is unlikely that 1 x 10-4 is within the limit of detection for an assay with only 16,600 Albumin counts. CDRH acknowledges that inclusion of this result will not have a major impact on the efficacy analyses that were provided by the sponsor. CDRH defers to CDER as to whether to consider sample (b) (6) as MRD(-) or MRD(+).

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