

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208573Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA #	NDA 208573
Product Name:	Venclexta (venetoclax)
PMR #1 Description: PMR# 3068-1	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 chronic lymphocytic leukemia (CLL), including CLL with deletion 17p.
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>completed</u>
	Trial Completion: <u>05/2018</u>
	Final Report Submission: <u>05/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Patients with CLL with deletion 17p have an unmet medical need. The response rates from single arm trials submitted to the application require confirmation of clinical benefit.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed PMR trial is to confirm and verify the clinical benefit of venetoclax in the treatment of patients with relapsed/refractory CLL who have received at least 1 prior therapy and have the 17p deletion.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized clinical trial titled patients with CLL with or without the 17p deletion mutation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory randomized trial to fulfill the requirements of 21CFR314 Subpart H.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208,573
Product Name: Venclexta[®] (Venetoclax)

PMR#2 Description: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety
PMR# 3068-2 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 Schedule Milestones:	Final Protocol Submission:	03/2016 <u>(completed)</u>
	Trial Completion:	<u>03/2017</u>
	Final Report Submission:	<u>12/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Venetoclax is predominantly metabolized by CYP3A4/5 in the liver. Increased venetoclax exposures (plasma concentrations) are likely to be seen in patients with hepatic impairment. A clinical trial evaluating venetoclax in patients with varying levels of hepatic impairment is planned. The final study report is required to allow for informative labeling recommendations including possible dose adjustments in patients with varying degrees of hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Increased venetoclax exposures are likely to be seen in patients with hepatic impairment. Increased venetoclax exposure would likely result in increased toxicities such as neutropenia, anemia, thrombocytopenia, diarrhea and infections. Results of the hepatic impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying degrees of hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial needs to assess the pharmacokinetics and safety of venetoclax in patients with mild, moderate, or severe hepatic impairment.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208,573
Product Name: Venclexta® (Venetoclax)

PMR#3 Description: Evaluate the effect of venetoclax co-administration on pharmacokinetics of a
PMR# 3068-3 probe substrate of P-gp. Submit a complete final study report with all
 supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	08/2016
	Trial Completion:	11/2016
	Final Report Submission:	06/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Venetoclax has inhibition potential on efflux transporter P-gp at therapeutic doses and concentrations. Concomitant administrations of drugs that are narrow therapeutic index P-gp substrates with venetoclax may significantly increase their exposures and result in intolerable adverse events. In order to determine the appropriate dose of narrow therapeutic index drugs that are P-gp substrates when co-administered with venetoclax, a clinical drug-drug interaction study will be required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Increased P-gp substrate exposures are likely when they are given concomitantly with venetoclax at proposed therapeutic dose levels. Results of the drug-drug interaction trial will allow for informative labeling recommendations including possible dose adjustments in patients who take narrow therapeutic index P-gp substrates concomitantly with venetoclax.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete trial protocol for review and concurrence by the Agency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

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The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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

/s/

BEATRICE A KALLUNGAL
04/11/2016

BARRY W MILLER
04/11/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208573 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Venclexta Established/Proper Name: venetoclax Dosage Form: Tablet Strengths: 10, 50, and 100 mg		
Applicant: AbbVie Inc. Agent for Applicant (if applicable):		
Date of Application: October 29, 2015 Date of Receipt: October 29, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: June 29, 2016		Action Goal Date (if different): April 29, 2016
Filing Date: December 28, 2015		Date of Filing Meeting: December 15, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Venetoclax is a B-cell lymphocyte-2 (BCL-2) inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; this includes patients with 17p deletion.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 110159, IND (b) (4) IND 115045

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: 5 Years					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only : Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

PREA				Orphan designation
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BCPA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Packaging Human Factors Report			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label	<input type="checkbox"/> Immediate container label	<input type="checkbox"/> Blister card	<input type="checkbox"/> Blister backing label	<input type="checkbox"/> Consumer Information Leaflet (CIL)	<input type="checkbox"/> Physician sample	<input type="checkbox"/> Consumer sample	<input type="checkbox"/> Other (specify)
	YES	NO	NA	Comment				
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>						
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
Other Consults	YES	NO	NA	Comment				
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: DMPP consult 12/10/2015; QT/IRT consult 11/6/2015</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
Meeting Minutes/SPAs	YES	NO	NA	Comment				
End-of Phase 2 meeting(s)? Date(s): 7/2/2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>						
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/22/2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>						
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>						

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 15, 2015

BACKGROUND: AbbVie Inc. submitted a New Drug Application (NDA 208573) for venetoclax, in accordance with section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA). The initial modules, nonclinical and quality, of this rolling submission were received on September 15, 2015 and the final module, clinical, was received on October 29, 2015.

Venetoclax is an orally bioavailable small molecule, B-cell lymphocyte-2 (BCL-2) inhibitor that restores programmed cell death in cancer cells. The proposed indication for venetoclax is for the treatment of patients with chronic lymphocytic leukemia (R/R CLL) who have received at least one prior therapy; this includes patients with 17p deletion.

On September 20, 2012, venetoclax received Orphan Drug Designation for the treatment of chronic lymphocytic leukemia. On April 27, 2015, venetoclax was granted Breakthrough Therapy Designation for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL).

Venetoclax is a new molecular entity being reviewed under the PDUFA V Program.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Beatrice Kallungal	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Lori Ehrlich	Y
	TL:	Virginia Kwitkowski	Y
Clinical Pharmacology	Reviewer:	Guoxiang (George) Shen	Y
	TL:	Bahru Habtemariam	Y

• Pharmacometrics	Reviewer:	Lian Ma	Y
	TL:	Nitin Mehrotra	Y
Biostatistics	Reviewer:	Qing Xu	Y
	TL:	Yuan-Li Shen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ramadevi Gudi	Y
	TL:	Christopher Sheth	Y
Product Quality (CMC) Review Team:	ATL:	Olen Stephens	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Monica Cooper	
• Drug Product	Reviewer:	Rajiv Agarwal	Y
• Process	Reviewer:	Peter Guerrieri	
• Microbiology	Reviewer:	TBD	
• Facility	Reviewer:	Ruth Moore	
• Biopharmaceutics	Reviewer:	Gerlie Gieser	
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Rowe Medina	Y
	TL:	Barbara Fuller	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nisha Patel	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Nicole Garrison	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	Y
	TL:		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
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<ul style="list-style-type: none"> ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> ● Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reasons: <ul style="list-style-type: none"> ○ the clinical study design was acceptable ○ the application did not raise significant safety or efficacy issues ○ the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>New Molecular Entity (NDAs only)</p>	

<ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments: Included in the 9/15/2015 submission</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	N/A
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): **1/27/2016**

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

BEATRICE A KALLUNGAL
03/25/2016

PATRICIA N GARVEY
03/25/2016

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208573

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Venclexta (venetoclax); 10, 50, and 100 mg Tablet

Applicant: AbbVie Inc.

Receipt Date: October 29, 2015

Goal Date: June 29, 2016

1. Regulatory History and Applicant's Main Proposals

AbbVie Inc. submitted a New Drug Application (NDA 208573) for venetoclax, in accordance with section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA). The initial modules, nonclinical and quality, of this rolling submission were received on September 15, 2015 and the final module, clinical, was received on October 29, 2015.

Venetoclax is an orally bioavailable small molecule, B-cell lymphocyte-2 (BCL-2) inhibitor that restores programmed cell death in cancer cells. The proposed indication for venetoclax is for the treatment of patients with chronic lymphocytic leukemia (R/R CLL) who have received at least one prior therapy; this includes patients with 17p deletion.

On September 20, 2012, venetoclax received Orphan Drug Designation for the treatment of chronic lymphocytic leukemia. On April 27, 2015, venetoclax was granted Breakthrough Therapy Designation for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL).

Venetoclax is a new molecular entity being reviewed under the PDUFA V Program.

As part of this NDA submission, the applicant also submitted the proposed US Prescribing Information (USPI) in Microsoft Word format.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant during labeling negotiations. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES

Selected Requirements of Prescribing Information

7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

NO 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The 4-digit year is missing*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A 35. All text in the BW should be **bolded**.

Comment:

- N/A 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- NO** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *The Medication Guide should be on the next page and not part of the package insert.*

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/s/

BEATRICE A KALLUNGAL
03/25/2016

PATRICIA N GARVEY
03/25/2016

**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: March 18, 2016

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)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Quick Start Guide (QSG)

Drug Name (established name): VENCLEXTA (venetoclax)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208573

Applicant: AbbVie Inc.

1 INTRODUCTION

On October 29, 2015, AbbVie Inc. submitted for the Agency's review the final portion of a rolling submission for New Drug Application (NDA) 208573 for VENCLEXTA (venetoclax) tablets. The proposed indication for VENCLEXTA (venetoclax) tablets is 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 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 December 10, 2015 and December 9, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Quick Start Guide (QSG) for VENCLEXTA (venetoclax) tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the QSG was completed January 26, 2016.

2 MATERIAL REVIEWED

- Draft VENCLEXTA (venetoclax) MG received on October 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 9, 2016.
- Draft VENCLEXTA (venetoclax) Prescribing Information (PI) received on October 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 9, 2016.
- Draft VENCLEXTA (venetoclax) QSG received on October 29, 2016, and received by DMPP and OPDP on March 14, 2016.
- Approved IMBRUVICA (ibrutinib) comparator labeling dated March 4, 2016.
- Division of Medication Error, Prevention, and Analysis (DMEPA) Label and Labeling Review of Venclexta (venetoclax) tablet, 10 mg, 50 mg, 100 mg dated January 26, 2016.

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. In our review of the MG and QSG the target reading level is at or below an 8th grade 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. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and QSG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and QSG are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and QSG are 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 and QSG meet 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 comparator labeling where applicable.
- The appended QSG incorporates DMPP and DMEPA input.

4 CONCLUSIONS

The MG and QSG are acceptable with our recommended changes.

The Word version of the QSG submitted by the Applicant is not sufficiently modifiable to allow for marked up revisions. Therefore, we are providing comments and recommended revisions to the QSG below in this document.

5 RECOMMENDATIONS

Comments specific to each section of the QSG:



9) Ensure consistency between the PI, MG, QSG, and packaging.

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and QSG 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 and QSG.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
03/18/2016

NISHA PATEL
03/18/2016

SHARON R MILLS
03/18/2016

LASHAWN M GRIFFITHS
03/18/2016

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

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

Memorandum

Date: March 17, 2016

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

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for [TRADENAME] (venetoclax) tablets, for oral use NDA 208573

In response to your consult dated December 9, 2015, we have reviewed the draft Package Insert (PI) for [TRADENAME] (venetoclax) tablets, for oral use (Venetoclax), and offer the following comments. Please note that OPDP has made these comments using the version e-mailed to OPDP on March 9, 2016.

Section	Statement from draft	Comment
Highlights, Warnings and Precautions	Immunization: Do not administer live attenuated vaccines (b) (4) TRADENAME treatment. (emphasis added)	We note that Section 5.3 of the full PI states, "Do not administer live attenuated virus vaccines (b) (4) treatment with TRADENAME until B-cell recovery occurs. " (emphasis added) OPDP recommends revising the Highlights, Warnings and Precautions section to ensure consistency with the Warnings and Precautions section (Section 5.3) of the full PI.
2 Dosage and Administration, 2.2 Risk Assessment and Prophylaxis for Tumor Lysis Syndrome	(b) (4)	Is the bolded term needed? While we note that this term is describing why TLS can occur, it is promotional in tone and could be used to overstate the efficacy of Venetoclax.

Section	Statement from draft	Comment
5 Warnings and Precautions, 5.1 Tumor Lysis Syndrome	(b) (4)	
2 Dosage and Administration, 2.5 Dose Modifications for Use with CYP3A and P-gp Inhibitors	Resume the TRADENAME dose that was used prior to initiating the (b) (4) 2 to 3 days after discontinuation of the inhibitor.	We note that Section 7.1 of the full PI states the following under (b) (4): “Resume the TRADENAME dose that was used prior to initiating the (b) (4) 2 to 3 days after discontinuation of the inhibitor.” Should (b) (4) be added to Section 2.5 of the full PI to ensure consistency with Section 7.1 of the full PI?
5 Warnings and Precautions, 5.1 Tumor Lysis Syndrome	Concomitant use of TRADENAME with strong or moderate (b) (4) increases venetoclax exposure and may increase the risk of TLS at initiation and during ramp-up phase.	We note that comment [SG11] states: “To applicant: (b) (4)” Should (b) (4) be added to this statement?
12 Clinical Pharmacology, 12.1 Mechanism of Action	Overexpression of Bcl-2 has been demonstrated in (b) (4) . . . In nonclinical studies, venetoclax has demonstrated cytotoxic activity in a (b) (4) . (emphasis added)	Is the bolded language needed? If not, please consider deleting as this could be used promotionally (b) (4)
14 Clinical Studies	(b) (4)	(b) (4)

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/s/

NISHA PATEL
03/17/2016

Clinical Inspection Summary

Date	March 9, 2016
From	Anthony Orenca M.D., F.A.C.P., Janice Pohlman M.D., M.P.H.
To	Lori Ehrlich, M.D., Virginia Kwitkowski, M.S., A.C.N.P.-B.C., Beatrice Kallungal
NDA	208573
Applicant	Abbvie Inc.
Drug	Venetoclax
NME	Yes
Therapeutic Classification/Designation	Priority (CDER Breakthrough Designation)
Proposed Indication	Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)
Consultation Request Date	November 23, 2015
Summary Goal Date	March 22, 2016
Action Goal Date	April 29, 2016
PDUFA Date	April 29, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Overall assessment and recommendation: data submitted by the inspected sites appear acceptable and reliable in support of this specific indication.

In summary, two clinical studies were submitted in support of the applicant's NDA. Three clinical sites (Drs. Wierda, Davids, and Coutre) were selected for inspection. The sponsor was also inspected.

The preliminary classification for the inspections of Drs. Davids and Coutre is No Action Indicated (NAI). The preliminary classification for the sponsor inspection is No Action Indicated. The final classification for the inspection of Dr. Wierda is Voluntary Action Indicated (VAI).

Based upon the inspection of three clinical sites and the sponsor, the data reported to the sponsor by these clinical sites and subsequently by the sponsor to the NDA appear to be reliable and may be used in support of the requested indication. The sponsor's oversight of the studies also appears to be adequate.

Observations noted above for the two clinical investigator sites and sponsor, are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

II. BACKGROUND

The 17p chromosomal deletion is an aberration of prognostic relevance in CLL and accounts for up to 30% of all relapsed/refractory subjects with CLL. Active treatments for the broader CLL population, such as fludarabine based regimens and alkylators are associated with poor response in the 17p patient population.

ABT-199 [*venetoclax*] is an orally available small molecule Bcl-2 family protein inhibitor. In vitro, ABT-199 demonstrated broad cell killing activity against a panel of lymphoma and leukemia cells. ABT-199 [*venetoclax*] was especially potent against cell lines expressing high levels of Bcl-2.

Two open-label randomized clinical trial studies were submitted in support of the applicant's NDA. For this NME NDA under the PDUFA V program review with priority therapy designation, two study protocols (M12-175 and M13-982) were part of the submission for which clinical site inspections were sought by CDER DHP. CDER DHP requested three domestic sites for inspection. The sites enrolled large numbers of patients and showed good response to treatment. The following overview of the two studies (Study M12-175 and Study M13-982) is intended as background context for interpreting the inspectional findings.

Study M12-175

M12-175 was a Phase 1, open-label, multicenter study evaluating the safety and PK profile of ABT-199 [*venetoclax*] under a once daily dosing schedule. Two arms were designed and implemented for dose escalation: Arm A, chronic lymphocytic leukemia/small lymphocytic leukemia and Arm B, non-Hodgkins lymphoma subjects.

The primary objectives of this study were to assess the safety profile, characterize pharmacokinetics (PK), determine the maximum tolerated dose (MTD), determine the recommended Phase 2 dose, and determine the lead-in period regimen of ABT-199 [*venetoclax*] in subjects with relapsed or refractory chronic lymphocytic leukemia and non-Hodgkin lymphoma.

CLL subjects had tumor response or clinical disease progression assessed using modified criteria adapted from the National Cancer Institute-Working Group (NCI-WG) Guidelines, as updated in 2008 by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) with the addition of CT imaging or magnetic resonance imaging (MRI). Non-Hodgkins Lymphoma (NHL) or Small Lymphocytic Lymphoma (SLL) subjects had tumor response or clinical disease progression assessed using the International Working Group (IWG) criteria. Overall response rate was considered the primary efficacy endpoint.

There were 9 principal investigators at 10 clinical study sites in the U.S. and Australia. The first subject's visit was on May 23, 2011. This Phase 1 clinical investigative study is still ongoing.

Per the sponsor's interpretation for this Phase 1 dose-escalation study, the estimated proportion of subjects with a durable response at 12 months was ^{(b) (4)} in the dose

escalation cohorts, with the rate greater in subjects treated with daily doses of 400 mg. The most significant adverse event/toxicity observed in this study was tumor lysis syndrome (observed in eight CLL/SLL subjects). Neutropenia and related events (decreased neutrophil count, febrile neutropenia) were the most notable adverse events, with half of 116 CLL/SLL subjects experiencing at least one neutropenia event. Gastrointestinal toxicities of diarrhea (~49%) and nausea (~47%) were other frequently reported adverse events and primarily low grade and manageable.

Study M13-982

Protocol M13-982 was a Phase 2, open-label, single arm study to determine the efficacy of ABT-199 (GDC-0199) [*venetoclax*] in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring 17p deletion.

The primary objective of the main cohort was to evaluate the efficacy of ABT-199 [*venetoclax*] monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia harboring the 17p deletion. Overall response rate was considered the primary efficacy endpoint. The safety cohort primary objective was to evaluate safety of ABT-199 [*venetoclax*] in ~50 subjects with relapsed/refractory or previously untreated CLL harboring 17p deletion per the updated tumor lysis syndrome (TLS) prophylaxis and management measures.

The study was conducted at 38 sites in the United States, Australia, Canada, France, Germany, Poland, and the United Kingdom. The first subject first visit was June 27, 2013. This Phase 2 study is still ongoing. Per sponsor's interpretation, the primary endpoint of overall response rate (a) over 60%, based on the Independent Review Committee assessment was met for both the first 70 subjects (77.1% overall response) and the total efficacy population of 107 (79.4% overall response), and (b) 73.8% overall response, as determined by the principal study site investigators.

III. RESULTS (by site):

Name of CI, Address.	Site #, Protocol # and # of Subjects	Inspection Date	Final Classification
William Wierda, M.D. Dept. of Leukemia, Unit 428 MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030	Site 35505 Study M12-175 Enrolled n=21 subjects Study M13-982 Enrolled n=1 subject	December 12 to 21, 2015	VAI
Matthew Davids, M.D. Dana Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215	Site 43157 Study M12-175 Enrolled n=17 subjects Study M13-982 Enrolled n=3 subjects	January 11 to 15, 2015	Preliminary: NAI

Name of CI, Address.	Site #, Protocol # and # of Subjects	Inspection Date	Final Classification
Steven Coutre, M.D. 875 Blake Wilbur Dr. Clinic C MC 5820 Stanford CA 94305	Site 38961 Study M13982 Enrolled n=6 subjects	February 29 to March 1, 2016	Preliminary: NAI
Abbvie Inc. 1 North Waukegan Road North Chicago, IL 60064	Protocol M12-175, Protocol M13-982	January 21, 2016 to February 4, 2016	Preliminary: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator**1. William Wierda, M.D.**

Houston, TX 77030

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from December 12 to 21, 2015.

For Study M12175, a total of 27 study subjects were screened and 21 subjects with CLL were enrolled in the study. Twelve study subjects discontinued from the study (including 7 subjects who died among the 12 patients who discontinued). Nine study subjects completed the study. An audit of 11 enrolled subjects' records was conducted.

For Study M13982, a single subject was screened, enrolled, and completed the study. An audit of this enrolled subject's records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

Specifically, serious adverse events were not reported to the sponsor within the two day time frame window for (1) Subject 235 died on [REDACTED] (b) (6), and the sponsor was made aware on December 17, 2015, (2) Subject 241 had a cardiac pacemaker procedure on [REDACTED] (b) (6), and the sponsor was made aware on July 23, 2015, and (3) Subject 273 had a hip fracture on [REDACTED] (b) (6), and the sponsor was made aware on December 2, 2014. These adverse events were all reported to the NDA submission.

Dr. Wierda's response to the Form FDA 483 letter on January 7, 2016 appeared adequate.

Notwithstanding the above regulatory deficiencies which were not critical, the study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

2. Matthew Davids, M.D.

Boston, MA 02215

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from January 11 to 15, 2016.

For Study M12175, a total of 22 study subjects were screened and 17 subjects were enrolled in the study. The study is ongoing; seven subjects are still actively participating in this study. An audit of the 17 enrolled subjects' records was conducted.

For Study M13982, four subjects were screened, three subjects enrolled, and one study subject remains on active treatment in the study. An audit of the 3 enrolled subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

3. Steven Coutre, M.D.

Stanford CA 94305

The inspection evaluated the following documents: source records, screening and enrollment

logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from February 29 to March 1, 2016.

For Study M13982, a total of 13 study subjects were screened, and 6 subjects were enrolled in the study. The study is ongoing; three study subjects are actively participating in the follow-up phase of the study. An audit of the enrolled subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

Sponsor inspection

4. Abbvie Inc.

North Chicago, IL 60064

The inspection was conducted from January 21, 2016 to February 4, 2016. This inspection covered sponsor practices related to Study M12-175 and Study M13-982. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors. Additionally the inspection covered monitoring of the three clinical investigator sites listed above, adverse event reporting and safety concerns, audit plans, quality assurance and data management plans.

In general, the sponsor practices appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection

Data submitted by this sponsor appear acceptable in support of the requested indication.

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

/s/

ANTHONY J ORENCIA
03/10/2016

JANICE K POHLMAN
03/10/2016

KASSA AYALEW
03/10/2016

HUMAN FACTORS, LABEL, AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 26, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 208573
Product Name and Strength:	Venclexta (Venetoclax) tablet, 10 mg, 50 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie, Inc
Submission Date:	October 29, 2015
OSE RCM #:	2015-2092
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

AbbVie, Inc. is developing Venclexta for the treatment of Chronic Lymphocytic Leukemia (CLL) under NDA 208573. Thus, the Division of Hematology Products (DHP) requested that DMEPA evaluate the Applicant's proposed wallet, blister pack labels and labeling, Prescribing Information (PI) and quick start guide (QSG). Additionally, AbbVie conducted a human factors validation study to evaluate the proposed wallet and blister packs. We evaluated the results from the validation study to help inform the labels and labeling of the product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Venclexta is an oral tablet used for the treatment of CLL. Venclexta is dosed in a ramp-up regimen, with patient's beginning treatment at 20 mg and slowly increasing to 50 mg, 100 mg, 200 mg and then to a 400 mg maintenance dose. The packaging for the ramp-up phase was designed in a Starting Pack. The Starting Pack is composed of an outer carton which contains 4 weekly wallets and QSG. Seven daily doses in a blister will be included in one wallet. Each wallet has an individual tear-off daily dose tab that is perforated and pulled off each day to reveal the blister pocket. For this product we evaluated the Applicant's PI, QSG, wallet system and its label as well as results of the Human Factors Study (HFS).

3.1 HUMAN FACTORS STUDY:

Methodology:

DMEPA reviewed methodology for the HFS on May 22, 2015¹ and found it acceptable in terms of objectives, participants, test scenarios, and training. We had provided recommendations to include information regarding dose interruption of more than 8 hours, but less than two weeks. We also recommended including a knowledge-based task to assess hydration days and to include the 800 phone number for questions on the Principal Display Panel (PDP) of the blister pack labeling. We have confirmed that our previous recommendations were adequately implemented.

Results:

In terms of usability, the human factors study results demonstrated that Venclexta starting pack QSG can be used safely and effectively by users as majority of participants on the study were able to use the product as intended without any failures. The failures that did occur in the study can be addressed through labels and labeling and do not require the change in the design of the product. Please see further discussion below that describes the failures that occurred during HF study.

Two types of failures occurred:

- Underdose (n=4)
- Misinterpretation of prep hydration instructions (n=2)

Underdose:

The first failure was related to dosing administration errors in four patients.

- Three participants only took one tablet on Week 1 Day 1 instead of two tablets. One of these three participants made the same mistake on Week 4 Day 7. The root cause of these failures was related to that one participant's previous mental understanding that when starting on any medication, one tablet is the standard dose. He comprehended that the dose for Week 1 and Week 4 was two tablets a day, but that did not influence his action and he took only one tablet. Since the patient participant comprehended the instructions, but did not follow them, we consider this to be a test artifact. The second participant did not perceive the second tablet in Week1 Day 1 blister cavity because she was rushing to complete the task which contributed to the failure. In addition, the third participant misread the instruction [REDACTED] (b) (4) as singular (tablet)

¹ Division of Hematology Products Type C Meeting Minutes. Silver Spring (MD): FDA, CDER, OND, DHP (US); 2015 MAY 27.

instead of plural (tablets). The second and third participant's failures were related to personal factors and not a result of labels, labeling, and QSG.

- The fourth participant did not take the tablet out of the packaging. Upon further probing, the participant expressed confusion about fast-forwarding dates on the calendar which likely contributed to him forgetting about simulating taking the tablets. In the real world patients would take medications daily and would not need to fast forward through dosing days. Since this failure was related to the artificial fast-forwarding of dates on the calendar, we consider this to be a test artifact.

Although the failures may have been related to test artifacts, we do note that the QSG can be improved to clearly identify the dose is 2 tablets for week 1 and 4. We provide recommendations in section 4.2 to increase the prominence of this information.

Misinterpretation of the prep hydration instructions:

Two participants misunderstood prep hydration to mean the two days at the hospital. This was due to misinterpretation of the task scenario instructions and QSG on prep hydration. They were assigned to the high risk scenario and in the simulated instructions; they would spend the first 2 days at the hospital. This led the participants to believe they would need to hydrate at home prior to starting the medication in the hospital. Despite reviewing the QSG, they were unable to understand that prep hydration referred to hydrating before the start of medication that included the two doses at the hospital.

- One participant misunderstood prep hydration days to be Days 6 and 7 of each week. The participant thought that (b) (4) were headers for Days 6 and 7 of each week (b) (4). After reviewing the blister pack and instructions stated on them, we agree that the visual display (b) (4) can easily be confused (b) (4) thus revisions are needed to the QSG.
- One participant misunderstood prep hydration to mean the two days at the start of each week when he needed to hydrate. The participant did not understand prep hydration meant hydrating prior to the start of medication and thought it meant hydrating the first 2 days of each week when consuming medication. Therefore, this error does not appear to relate to the packaging of the product. By the time a patient obtains the actual product in the starting pack, they may be under impression that they are to start the product right away. Thus, it appears prudent that patient education is provided by the healthcare provider regarding the proper hydration prior to therapy initiation. Therefore, the PI should clearly state that providers should educate the patient about initiating prep hydration 2 days prior to starting therapy.

Labels and Labeling:

Upon review of the container label and carton labeling submitted by the Applicant, we noted the following areas for improvement:

- Readability of the Dosage and Administration in the prescribing information, container labels, and carton labeling.

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Summative Study demonstrated that the intended user population can use Venclexta starting pack with Quick Starting Guide (QSG) safely and effectively. However, we identified areas in the proposed labels and labeling that AbbVie can improve to increase clarity and prominence of important information to promote the safe use of this product. These changes to the user interface do not require an additional human factors validation study. See Section, 4.1, below, for our recommendations.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Revise all instances of the “TRADENAME” to the conditionally acceptable proprietary name VENCLEXTA.
2. In section 2.3 (Risk Assessment and Prophylaxis for Tumor Lysis Syndrome)
 - a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
 - i. Revise the abbreviations “≥” to read “greater than or equal to”, “-“ to read “to”, and “<” to read “less than”.
3. We note inconsistencies in the requirements for oral hydration in the prescribing information and the labeling. In the wallet system labeling, it states to (b) (4)
. In the PI it is recommended to drink 6-8 glasses of water each day. To mitigate the potential for administration errors, we recommend having consistent instructions on oral hydration requirements across all labeling.

4.2 RECOMMENDATIONS FOR THE ABBVIE

We recommend the following be implemented prior to approval of this NDA:

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 October 21]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

A. Monthly Blister Carton

1. Ensure the NDC number is included on the carton. Currently the NDC is denoted by a place holder NDC. However, the NDC number is contained in the prescribing information.
2. Wallet and blister pack labeling
 - a. Inside flap of Week 1
 - i. See A.1 and revise the wallet and blister pack labeling accordingly.
 - ii. To enhance patient comprehension, consider use patient-friendly language. For example, instead of the word (b) (4) use the more patient friendly term, “before”. This term is used consistently throughout the QSG.
3. (b) (4) Please relocate the drug barcode to a visible location on carton labeling as it is often used as an additional verification during the pharmacy procurement process.

B. Weekly Wallet, Unit Dose Pack, and Bottle labeling

1. See A.1 and revise the wallet, unit dose pack, and bottle labeling accordingly.
2. Include the following cautionary statement on the PDP: “Dispense the accompanying Medication Guide to each patient.”
3. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 201.17 and 21 CFR 201.10(i)(1).
4. We recommend adding the NDC number in the top third of the principal display panel since it provides additional means of ensuring the correct product is selected.
5. We note inconsistencies in the requirements for oral hydration in the prescribing information and the labeling. In the wallet system labeling, it states to (b) (4)
(b) (4). In the PI it is recommended to drink 6-8 glasses of water each day. To mitigate the potential for administration errors, we recommend having consistent instructions on oral hydration requirements across all labeling.
6. Inside the Week 1 and Week 4 wallet revise the statement (b) (4)
(b) (4) to “Push down on **both** tablets to remove” to ensure this important information is prominent.

C. Quick Start Guide

1. In the row: “Before 1st Dose”
 - a. We recommend deleting the boxes that say (b) (4)
(b) (4)
(b) (4) Patients should be instructed to write in the day of the week and date for each Prep Day, and each day during Weeks 1 through 4. This will help ensure that patients do not

inadvertently take a dose twice. (b) (4)

add a reminder to patients that states, “Prep Day 1 and Prep Day 2 are the 2 days before the first dose of Venclexta, as directed by your healthcare provider.”

2. In the box for each day, below the revised picture of the tablets, add the following bolded text:

Each day of Week 1, add the statement: **Take two 10 mg tablets**

Each day of Week 2, add the statement: **Take one 50 mg tablet**

Each day of Week 3, add the statement: **Take one 100 mg tablet**

Each day of Week 4, add the statement: **Take two 100 mg tablets**

3. For consistency with the packaging of the product
 - a. Some information has been carried over from the Quick Start Guide to the packaging, for example, the inside flaps for each weekly pack of tablets and cardboard pull tabs for each daily dose. We recommend revising this information to be consistent with the revisions to the QSG, to the extent possible.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Venclexta that AbbVie submitted on October 29, 2015.

Table 2. Relevant Product Information for Venclexta	
Initial Approval Date	N/A
Active Ingredient	Venetoclax
Indication	For the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; this includes patients with 17 p deletion.
Route of Administration	Oral
Dosage Form	Tablet
Strength	10 mg, 50 mg, 100 mg
Dose and Frequency	Initiate therapy with Venclexta at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg.
How Supplied	This product is supplied as tablets of 10 mg, 50 mg, and 100 mg strengths; packaged in blister packs for the dose escalation period and in bottles for dosing at the recommended daily dose.
Storage	This product should be stored at (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 17, 2015, we searched the L: drive and AIMS using the terms, Venclexta to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous name review³ and Type C Meeting Minutes⁴.

³ Mistry M. Proprietary Name Review for Venclexta (IND 110159). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 25. 9 p. OSE RCM No.: 2015-191145.

⁴ Division of Hematology Products Type C Meeting Minutes. Silver Spring (MD): FDA, CDER, OND, DHP (US); 2015 MAY 27.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Results

Critical tasks: Participants performance was scored as success if they administered the correct dose. Out of the 30 participants tested in either group, 26 successfully completed all critical tasks. Three participants only took one tablet on Week 1 Day 1 instead of two tablets. One of these participants made the same mistake on Week 4 Day 7.

Essential tasks: Participants performance was scored as success if they completed hydration, contacting their HCP and what to do if they missed a dose. There were four failures recorded on essential tasks due to failure to mention hydration.

Untrained Adults

Table 2. Summary of Successes: Critical Tasks

Critical Tasks	Success Rate (N=30)
Task 1, Week 1 Dose	27 (90%)
Task 2, Week 2 Dose	29 (97%)
Task 3, Week 3 Dose	30 (100%)
Task 4, Week 4 Dose	29 (97%)

Table 3. Summary of Successes: Essential Tasks

Essential Tasks	Success Rate (N=30)
Indicates contacting HCP before starting therapy	30 (100%)
Comprehends prep hydration	26 (87%)
Comprehends hydration on other relevant days	30 (100%)
Comprehends what to do for a missed dose	30 (100%)

Table 4. Participant performance on Critical and Essential Tasks (High Risk Arm)

P#	Critical Tasks (Performance Based)				Essential Tasks (Knowledge Assessment Based)			
	Task 1 – Week 1 Day 3	Task 2 – Week 2 Day 4	Task 3 – Week 3 Day 1	Task 4 – Week 4 Day 7	Indicates contacting HCP before starting therapy	Comprehends Prep Hydration	Comprehends Hydration on other relevant days	Comprehends what to do for a missed dose
P01	Success	Success	Success	Success	Success	Success	Success	Success
P03	Success	Success	Success	Success	Success	Success	Success	Success
P05	Success	Success	Success	Success	Success	Success	Success	Success
P07	Success	Success	Success	Success	Success	Success	Success	Success
P09	Success	Success	Success	Success	Success	Success	Success	Success
P11	Success	Failure*	Success	Success	Success	Failure	Success	Success
P13	Success	Success	Success	Success	Success	Failure	Success	Success
P15	Success	Success	Success	Success	Success	Success	Success	Success
P17	Success	Success	Success	Success	Success	Success	Success	Success
P19	Success	Success	Success	Success	Success	Success	Success	Success
P21	Success	Success	Success	Success	Success	Success	Success	Success
P23	Success	Success	Success	Success	Success	Success	Success	Success
P25	Success	Success	Success	Success	Success	Failure	Success	Success
P27	Success	Success	Success	Success	Success	Success	Success	Success
P29	Success	Success	Success	Success	Success	Success	Success	Success

* Test Artifact

Table 5. Participant performance on Critical and Essential Tasks (Low Risk Arm)

P#	Critical Tasks (Performance Based)				Essential Tasks (Knowledge Assessment Based)			
	Task 1 – Week 1 Day 1	Task 2 – Week 2 Day 1	Task 3 – Week 3 Day 5	Task 4 – Week 4 Day 7	Indicates contacting HCP before starting therapy	Comprehends Prep Hydration	Comprehends Hydration on other relevant days	Comprehends what to do for a missed dose
P02	Success	Success	Success	Success	Success	Success	Success	Success
P04	Failure	Success	Success	Failure	Success	Success	Success	Success
P06	Success	Success	Success	Success	Success	Success	Success	Success
P08	Success	Success	Success	Success	Success	Success	Success	Success
P10	Success	Success	Success	Success	Success	Success	Success	Success
P12	Failure	Success	Success	Success	Success	Success	Success	Success
P14	Success	Success	Success	Success	Success	Success	Success	Success
P16	Failure	Success	Success	Success	Success	Success	Success	Success
P18	Success	Success	Success	Success	Success	Success	Success	Success
P20	Success	Success	Success	Success	Success	Success	Success	Success
P22	Success	Success	Success	Success	Success	Success	Success	Success
P24	Success	Success	Success	Success	Success	Success	Success	Success
P26	Success	Success	Success	Success	Success	Success	Success	Success
P28	Success	Success	Success	Success	Success	Success	Success	Success
P30	Success	Success	Success	Success	Success	Failure	Success	Success

Analysis of Task Failures:

Table 6. Failure Description and Root Cause Analysis for Critical Tasks (Continued)

Subject	P04				
Subject Description	Prostate Cancer	Low Risk	Male, 69	Instructions Used: None	NVS of 0/6
Failure Description	Participant took only one of the two tablets for the Week 4 Day 7 dose.				
Root Cause	Primary: Mental Model of 'Lowest Possible Dose' Secondary: Potential Low Literacy				
Observed Behavior	The participant did not read the QSG or any other instructions on the weekly booklets. He proceeded to remove one of the two tablets for the Week 4 Day 7 dose and stated he was done with the task.				
Participant Explanation	The participant explained that "I have been taking one a day all the time so I would not want to start taking two at the end of it (referring to end of the week)." He was able to articulate that the 14 tablets for Week 4 indicated he would have to take two tablets a day but was unable to correlate that with his actions.				
Root Cause Analysis	From the start of the session as demonstrated by his performance on Task 1 when he took only one of the two tablets for Week 1, the participant seemed to be working with the idea that he needed to take only one tablet a day. Despite the moderator's explanation that he had been taking two tablets a day for his dose for both Week 1 and 4, he was unable to grasp the concept of taking two tablets a day during Week 4. Moreover, he did not read the QSG or other instructions that may have helped him understand the dosage for these weeks. This participant was also coded as low health literacy per the NVS, which is likely to have affected his comprehension of moderator instructions and an overall understanding of dosage as it relates to taking medication for each of the 4 weeks. He had been taking only one tablet a day for Weeks 2 and 3 and this is likely to have led him to take only one tablet in Week 4.				
Clinical Impact of Failure	The participant's actions would result in a Week 4, Day 7 dose of 100 mg instead of the intended 200 mg. The clinical impact of this failure depends on if it demonstrates a pattern of underdosing during the ramp-up dosing period. This participant failed two of the four dosing tasks; this could indicate continual underdosing during the ramp-up which may increase risk of TLS when a patient would be started on the treatment dose.				

Table 6. Failure Description and Root Cause Analysis for Critical Tasks

Subject	P04				
Subject Description	Prostate Cancer	Low Risk	Male, 69	Instructions Used: Weekly Booklet panel	NVS of 0/6
Failure Description	Participant took only one of the two tablets for the Week 1 Day 1 dose.				
Root Cause	Primary: Mental Model of 'Lowest Possible Dose' Secondary: Potential Low Literacy				
Observed Behavior	The participant opened the booklets and briefly read the instructions on the inside panel of the booklet. He proceeded to remove the tablets, struggled to retrieve the first of the two tablets and after doing so, stated he had taken the one tablet for his dose and simulated drinking water. At no point before or during this task did the participants read any instructions on the QSG.				
Participant Explanation	During probing, the participant explained that he did not realize he needed to take more than one tablet because if he were taking it weekly, it would be one tablet a day because two would be "overdose or too much." He added that the (simulated) doctor prescribed for him to take medication only once a day but was unable to explain any further. He looked at the instructions on the booklet and stated it did not say how many tablets he needed to take. He added that the way it is packaged, he would need to take two tablets a day but he took one tablet and thought that "one would be enough."				
Root Cause Analysis	The participant worked with a mental model of one tablet a day corresponding to the lowest possible dose for starting on any medication and accordingly took only one of the two tablets for the dose. He did not read the QSG. The participant stated he was told to take the medication once a day during the role-play but a review of the video confirmed this did not happen. This participant engaged in 'storytelling' in responding probing questions to explain his actions according to his mental model.				
Clinical Impact of Failure	This failure is not associated with harm and is of minimal clinical significance. The participant's actions would result in a Week 1, Day 1 dose of 10mg instead of the intended 20 mg. While an underdose, there is minimal risk in this failure because it is on the first day of the ramp-up dosing period. The ramp-up dosing is purposefully intended as underdosing to the intended treatment dose. Taking an even lower dose on Week 1, Day 1 is unlikely to affect treatment and would not result in increased risk.				

Table 6. Failure Description and Root Cause Analysis for Critical Tasks (Continued)

Subject	P11				
Subject Description	Stomach/Colon Cancer	High Risk	Male, 72	Instructions Used: QSG, Monthly booklet panel	NVS of 5/6
Failure Description	Participant did not take the tablet out of the packaging.				
Root Cause	Test Artifact Due to Confusion Regarding Fast-forwarding				
Observed Behavior	The participant expressed confusion regarding the dates on the calendar and how those mapped to the days on the weekly booklets, as well as regarding the "missing" tablets for the first 2 days of the week (referring to the first two doses taken in the hospital). He stated that it was not a water day and that he would take the tablets and check off (on the calendar) that he has taken them. He did not take the tablets out of the booklet and stated he was done with the task.				
Participant Explanation	During probing, when asked to explain his simulation of taking the dose for that particular day, he stated that "In my mind, I took it I guess I didn't physically take it." He added that during the task he was confused about the days (on the calendar versus the weekly booklet) and said that if he was actually taking a dose each day, he would not be confused about what tablets to take next.				
Root Cause Analysis	The participant expressed confusion about the mapping of calendar dates onto the days on the monthly booklet during the fast-forwarding exercise. It was clear from his actions and explanation that he forgot to simulate taking the tablets out of the booklet because of this distraction. Since it took the participant a few minutes to understand the calendar simulation, this confusion is likely to have contributed to him forgetting about simulating taking the tablets.				
Clinical Impact of Failure	N/A				

Table 6. Failure Description and Root Cause Analysis for Critical Tasks (Continued)

Subject	P12				
Subject Description	Ovarian Cancer	Low Risk	Female, 60	Instructions Used: QSG	NVS of 3/6
Failure Description	Participant took only one of the two tablets for the Week 1 Day 1 dose.				
Root Cause	Participant did not perceive second tablet in Week 1 Day 1 blister cavity				
Observed Behavior	The participant removed one of the two tablets for the Week 1 Day 1 dose, simulated drinking water, and stated she had taken her medication. During the task, she did not reference the QSG.				
Participant Explanation	During post-task probing, the participant stated she saw the two tablets in there but "somehow, I don't know why I only took one." She further explained, "I probably wasn't thinking. It depends. It was early in the morning. I was rushing." The participant clarified that she was talking about the morning of the test session. She looked at the booklet instructions and said that the instructions did not tell her she needed to take two tablets, and that "since there weren't any instructions" she would call the doctor to ask how many she needed to take.				
Root Cause Analysis	Participant did not perceive second tablet in Week 1 Day 1 blister cavity because as self-reported, she was rushing to complete the task. Participant did not refer to any packaging materials while completing the task that may have allowed her to perceive the second tablet.				
Clinical Impact of Failure	This failure is not associated with harm and is of minimal clinical significance. The participant's actions would result in a Week 1, Day 1 dose of 10mg instead of the intended 20 mg. While an underdose, there is minimal risk in this failure because it is on the first day of the ramp-up dosing period. The ramp-up dosing is purposefully intended as underdosing to the intended treatment dose. Taking an even lower dose on Week 1, Day 1 is unlikely to affect treatment and would not result in increased risk.				

Table 6. Failure Description and Root Cause Analysis for Critical Tasks (continued)

Subject	P16				
Subject Description	Breast Cancer	Low Risk	Female, 55	Instructions Used: Weekly booklet panel	NVS of 6/6
Failure Description	Participant took only one of the two tablets for the Week 1 Day 1 dose.				
Root Cause	Primary: Misread Opening Instructions (b) (4) Secondary: (u) (4)				
Observed Behavior	Although the participant stated she would read the QSG, during the task she did not read the QSG. She opened the weekly booklet and read the information on the inside panel. She struggled to remove the tab, but once she was able to do so she then read the instructions aloud as, (b) (4) when the instruction actually says (b) (4). She had difficulty (b) (4) to remove the tablets. She flipped the booklet and punched one tablet out from the back and stated she was done with the task.				
Participant Explanation	The participant explained that she "probably didn't notice it that first time" and that she was "too busy trying to get the thing (tablet) out of there." She said that "I don't want to say I didn't see it but, I didn't see it and [I was] too busy trying to get this thing out of there (the other tablet) and just moved on."				
Root Cause Analysis	The participant did not read the QSG and relied on the inside of Weekly Booklet for instruction. The participant misread the instruction (b) (4) as singular (tablet) instead of plural (tablets). The participant's comments suggested a secondary root cause being difficulty and distraction (b) (4).				
Clinical Impact of Failure	This failure is not associated with harm and is of minimal clinical significance. The participant's actions would result in a Week 1, Day 1 dose of 10mg instead of the intended 20 mg. While an underdose, there is minimal risk in this failure because it is on the first day of the ramp-up dosing period. The ramp-up dosing is purposefully intended as underdosing to the intended treatment dose. Taking an even lower dose on Week 1, Day 1 is unlikely to affect treatment and would not result in increased risk.				

Table 7. Failure Description and Root Cause Analysis for Essential Tasks

Subject	P11				
Subject Description	Stomach/Colon Cancer	High Risk	Male, 72	Instructions Used: QSG, Monthly booklet panel	NVS of 5/6
Failure Description	Participant misunderstood prep hydration to mean the two days at the hospital.				
Root Cause	Misinterpretation of Task Scenario Instructions				
Observed Behavior	N/A				
Participant Explanation	The participant stated that prep hydration referred to hydrating during the 2 days that he would spend at the hospital, and that the hospital would make sure he stayed hydrated. During probing, he stated that nothing on the QSG specifically caused him to think that the days in the hospital were the same as the prep hydration days. He referred back to the (simulated) doctor's instructions at the beginning of the session and stated that "somebody's instructions were that the first 2 days would be at the hospital."				
Root Cause Analysis	The participant misunderstood prep hydration to mean he would need to hydrate on the first 2 days at the hospital. He was assigned to the high risk scenario and the (simulated) doctor's instructions that he would spend the first 2 days at the hospital led him to think those were the days that he would need to hydrate prior to starting medication on his own at home. Despite reviewing the QSG, he was unable to understand that prep hydration referred to hydrating before the start of medication that includes the two doses at the hospital.				
Clinical Impact of Failure	This failure is of minimal clinical impact because in this use scenario it would be mitigated by the risk controls in-place for prophylaxis management of TLS for high risk patients hospitalized at the beginning of treatment. Patient hydration is a standard component of TLS prophylaxis. If an HCP determines a patient's risks for TLS are significant to warrant in-patient initial dosing as in the high-risk scenario, the patient may be provided IV fluids as part of treatment initiation with the need for hydration being the responsibility of the HCP. Multiple risk minimization measures are being instituted to systematically ensure that the physician is involved in all key aspects TLS mitigation.				

Table 7. Failure Description and Root Cause Analysis for Essential Tasks (Continued)

Subject	P13				
Subject Description	Myeloma	High Risk	Male, 76	Instructions Used: QSG	NVS of 5/6
Failure Description	Participant misunderstood prep hydration to mean the two days at the hospital.				
Root Cause	Misinterpreted QSG on prep hydration				
Observed Behavior	N/A				
Participant Explanation	<p>This participant described a clear understanding of the need to continually hydrate daily for the first 30 days by drinking water throughout each day. The participant made multiple statements that he would drink the recommended amount of water each day. These included his statement when referring to the QSG of "Actually, what it is saying is try to drink plenty of water on all the days that you are taking this medication because it is very important to stay hydrated. Responding to what he understood specifically by 'prep days' he stated "that's when you start the medication and you are at the doctor's office Prep Day 1 and 2 you are being monitored in the hospital or the doctor's office before you get on your own to take the medication". He additionally referred to specific sections of the QSG that contains this information and described that he would drink at (b) (4) water every day and stated that the information on the QSG is a reminder for drinking plenty of water throughout treatment. After being pointed to the QSG calendar days marked prep hydration, he stated that "[It's] just a reminder to me for drinking plenty of water, it's not telling me the specific time to drink water, it's telling me to stay hydrated all through the 30 days of treatment.</p>				
Root Cause Analysis	<p>The participant misunderstood prep hydration to mean that he would need to hydrate the first 2 days at the hospital. He was assigned to the high risk scenario and interpreted the (simulated) doctor's instructions that he would take the first two doses at the hospital to mean those were the same days she would need to hydrate. Although he reviewed the calendar side of the QSG with the days marked for prep hydration, he was unable to understand that prep hydration referred to hydrating prior to the start of medication at the hospital.</p>				
Clinical Impact of Failure	<p>This failure is of minimal clinical impact because this participant clearly understood the need to continually hydrate daily for the first 30 days by drinking water throughout each day. If a patient was to take this course of action, there is no increase to the risk of TLS due to lack of hydration. If an HCP determines a patient's risks for TLS are significant to warrant in-patient initial dosing as in the high-risk scenario, the patient may be provided IV fluids as part of treatment initiation with the need for hydration being the responsibility of the HCP.</p>				

Table 7. Failure Description and Root Cause Analysis for Essential Tasks (Continued)

Subject	P25				
Subject Description	Breast/Colon Cancer	High Risk	Female, 61	Instructions Used: QSG	NVS of 5/6
Failure Description	Participant misunderstood prep hydration days to be Days 6 and 7 of each week.				
Root Cause	Misinterpreted QSG on prep hydration				
Observed Behavior	N/A				
Participant Explanation	When asked to interpret prep days, the participant began by saying they are the first 2 days of that particular 'mg' of the medication. She then pointed to Days 6 and 7 on the QSG and speculated it may mean the last 2 days of each week. She thought prep days are Days 6 and 7 because those were the "only 2 days when you are drinking the water back to back." The participant was confused by the QSG organization. "I can see someone thinking that this would be the prep day (pointing to Days 6 and 7 on Week 1 of the QSG)."				
Root Cause Analysis	The participant thought that (b) (4) were headers for Days 6 and 7 of each week (b) (4). This led to her misunderstanding that prep hydration occurs on Days 6 and 7 of each week. The organization of the QSG calendar columns suggest to her that every week's Days 6 and 7 were also prep days in addition to the actual prep days.				
Clinical Impact of Failure	This failure is of minimal clinical impact because in this use scenario it would be mitigated by the risk controls in-place for prophylaxis management of TLS for in-patients. Patient hydration is a standard component of TLS prophylaxis. If an HCP determines a patient's risks for TLS are significant to warrant in-patient initial dosing as in the high-risk scenario, the patient may be provided IV fluids as part of treatment initiation with the need for hydration being the responsibility of the HCP. Multiple risk minimization measures are being instituted to systematically ensure that the physician is involved in all key aspects TLS mitigation.				

Table 7. Failure Description and Root Cause Analysis for Essential Tasks (Continued)

Subject	P30				
Subject Description	Prostate Cancer	Low Risk	Male, 71	Instructions Used: QSG	NVS of 3/6
Failure Description	Participant misunderstood prep hydration to mean the two days at the start of each week when he needed to hydrate.				
Root Cause	Misunderstanding of Prep Hydration				
Observed Behavior	N/A				
Participant Explanation	Participant misunderstood prep to mean he was "preparing for something and I don't know what I am preparing for other than getting ready to drink 8 glasses of water." He thought prep Day 1 meant Day 1 of the dose and prep meant preparing for each day of medication. He added that the QSG markings (b) (4) were "inconsistent" and that they needed to be (b) (4)				
Root Cause Analysis	The participant interpreted prep hydration generally as preparing to take medication by drinking water. He did not understand prep hydration meant hydrating prior to the start of medication and thought it meant hydrating the first 2 days of each week when consuming medication. He was led to believe prep hydration happens during and not prior to the start of medication administration by what he saw as incorrect (b) (4) placements on the QSG calendar.				
Clinical Impact of Failure	In this situation, a patient would not have recognized the need to purposefully hydrate the 2 days before starting venetoclax, but would drink 8 glasses of water on the first day of treatment. While prep hydration is recommended, if skipped, there is no harm if the patient hydrates as recommended on the day of dosing.				

Subjective Assessment- Post Simulation Interview for critical tasks:

Additionally, during subjective feedback, participants rated the ease or difficulty of accessing the tablets within the booklet. Although participants were able to easily remove the booklet from the monthly carton and open the booklet, they had difficulties removing smaller tablets from Week 1 and 3 booklets. The average rating of ease or difficulty was given 3 on a five point scale (1-5). The booklet was previously evaluated for (b) (4) packaging and senior adult use effectiveness ((b) (4) SAUE) and passed the requirements. Since the booklet was tested in (b) (4) SAUE, we think this is acceptable and does not preclude concerns at this time.

Table 8. Average Ratings on Subjective Assessment

Post-Task Subjective Assessment	Average Rating
Ease or difficulty of removing booklet from monthly carton	4.6
Ease or difficulty of opening a booklet	4.5
Ease or difficulty of accessing the tablets from within the booklet	3.0

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

/s/

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01/26/2016

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