

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208573Orig1s000

CHEMISTRY REVIEW(S)



Recommendation: Approval

**NDA 208573
Review #1**

Drug Name/Dosage Form	Venetoclax/Tablet
Strength	10, 50, 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
	Rolling	CMC

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	OPQ/ONDP/DNDAPI/BI
Drug Product	Rajiv Agarwal	OPQ/ONDP/DNDPI/BII
Process	Pete Guerrieri	OPQ/OPF/DPA1/BII
Microbiology		
Facility	Ruth Moore	OPQ/OPF/DIA/BI
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Rabiya Laiq	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Tracey Rogers	OPQ/ONDP/DNDPI/BII
Laboratory (OTR)		
ORA Lead		
Environmental Assessment (EA)	Rajiv Agarwal	OPQ/ONDP/DNDPI/BII

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)			(b) (4)
	Type III			Active	Adequate	
	Type III			Active	Adequate	By Rapti Madurave for NDA 50795 on 12-JAN-2005
	Type III			Active	Adequate	By Rajiv Agarwal for this NDA on 24-FEB-2016
	Type III			Active	Adequate	By Craig Bertha for NDA (b) (4) on 01-AUG-2005
	Type IV			Active	Adequate	By Rajiv Agarwal for this NDA on 24-FEB-2016
	Type IV			Active	Adequate	By Rajiv Agarwal for this NDA on 24-FEB-2016

* Due to the system Error in DARRTS for the DMF (b) (4), electronic submission of the review in DARRTS and its concurrence was not performed by this reviewer and Branch Chief, Ananmitro Banerjee. Individual components of the color coating are described in this review. The individual components meet the current USP/NF requirement and have been used in other FDA approved products.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology		Adequate		
CDRH				
Clinical				
Other				

Executive Summary

A. Recommendation and Conclusion on Approvability

NDA 208573 for Venclexta™ (venetoclax) tablets is recommended for approval by the Office of Pharmaceutical Quality. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “approve” recommendation was entered into Panorama 04-04-2016.

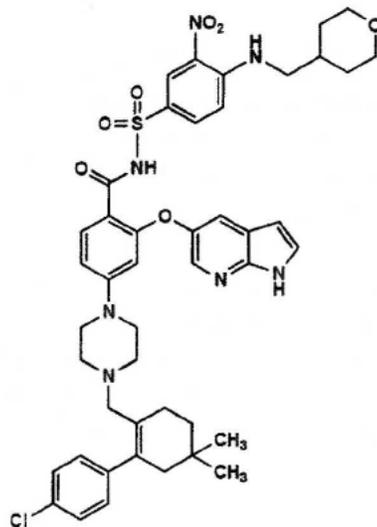
Based on the adequate totality of stability data at 24 months at long term storage conditions, 24 months of expiration dating may be granted for this product when stored at or below 30°C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

I. Summary of Quality Assessments

A. Drug Substance [Venetoclax] Quality Summary

1. Chemical Name (IUPAC): 4-(4-{{2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide



Venetoclax drug substance is a light yellow to dark yellow powder with a melting point onset of approximately 138°C. Venetoclax is not hygroscopic. (b) (4)



(b) (4)

(b) (4). Starting materials are fully characterized. The description of the drug substance manufacturing process and controls for starting materials, solvents, reagents, (b) (4) are adequate. Adequate in process controls are in place for the critical quality attributes during the drug substance manufacturing process. The drug substance is packaged in an (b) (4) and (b) (4). Stability data is provided for the drug substance in this packaging configuration. Long term and accelerated stability study results show no significant changes. Based on 24 months of long term data provided, a (b) (4) (b) (4) retest date for venetoclax drug substance is acceptable when stored in (b) (4) at or below 30°C.

B. Drug Product [Venetoclax] Quality Summary

Venetoclax tablets are available in 10, 50, or 100 mg strengths (b) (4) (b) (4). Drug product is supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet is debossed with “V” on one side and “10”, “50” or “100” corresponding to the tablet strength on the other side.

Excipients include copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. The tablet coating contains polyethylene glycol, talc, polyvinyl alcohol, titanium dioxide and either iron oxide yellow (for the 10 mg and 100 mg tablet) or iron oxide yellow, red and black (for the 50 mg tablet).



(b) (4)

(b) (4)

The commercial primary packaging configurations are either 120-count of 100 mg tablets in a 200 cc HDPE bottle with induction-sealed, (b) (4) (b) (4) cap, or 1 tablet in a blister (b) (4) (b) (4)

(b) (4) for (b) (4) 50, and 100 mg tablets. The stability studies on primary stability batches showed that 10 mg tablets packaged in the (b) (4), and 50 and 100 mg tablets packaged in the blister are physically and chemically stable during storage. In addition, the packaging configurations provide adequate protection of the product from (b) (4) such that the (b) (4) (b) (4) will be maintained below the proposed commercial shelf life limit over the duration of the shelf life.

The expiration-dating period of 24 months may be granted for the drug product packaged in either bottles or blisters and stored at or below 30°C.

Drug substance and drug product manufacturing facilities were reviewed as summarized in the tables below:

Drug Substance

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
AbbVie Ireland NL B.V	3004364014	Drug Substance manufacture and release testing	Medium product risk associated with NME	Acceptable	Approve based on profile and compliance history
(b) (4)			Low risk	Acceptable	Approve based on profile and compliance history
AbbVie Inc. 1401 Sheridan Rd North Chicago, IL	1411365	CTX Drug Substance Stability Testing	Low risk	Acceptable	Approve based on profile and compliance history
(b) (4)			Low risk	Acceptable	Approve based on profile and compliance history
(b) (4)			Low risk	Acceptable	Approve based on profile and compliance history

Drug product

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
AbbVie Ireland NL B.V	3004364014	TCM Drug Product Manufacture	Relatively low process risk in (b) (4)	Acceptable	Approve
AbbVie Deutschland GMBH & CO.KG	3002807401	TCM Drug Product (b) (4)		Acceptable	Approve based on compliance history and mitigation of the identified risks by (b) (4)
AbbVie Inc.	1411365	CTX Drug Product release testing and stability testing	Low risk	Acceptable	Approve based on compliance history
AbbVie Inc. 1N Waukegan Rd, Northern Chicago, IL	3009751352	TCM Drug Product primary packaging	Low risk	Acceptable	Approve based on compliance history

Based on the review of the application, inspection documents and compliance history of the drug substance and drug product manufacturing facilities, and the control testing laboratories, there are no significant outstanding risks that impact their ability to perform the functions listed in this application. All facilities are recommended for approval.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Venclexta
Non Proprietary Name of the Drug Product	Venetoclax tablets
Non Proprietary Name of the Drug Substance	Venetoclax
Proposed Indication(s) including Intended Patient Population	For the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.
Duration of Treatment	Until disease progression or unacceptable toxicity is observed
Maximum Daily Dose	400 mg
Alternative Methods of Administration	none

D. Biopharmaceutics Considerations

1. BCS Designation: N/A

- Drug Substance: low solubility (< 0.0042 mcg/mL dissolves in pH 4 and pH 7.4 at 25 °C); low-to-moderate permeability (In Mass-Balance Study, at least 20% radioactivity could be recovered as unchanged drug in the feces. Absolute BA study cannot be done (b) (4)

- Drug Product: (b) (4)

2. Biowaivers/Biostudies

- Biowaiver Requests - none
- PK studies – refer to the Clinical Pharmacology review
- IVIVC - none

From a Biopharmaceutics perspective, the NDA is recommended for approval. The following dissolution method and acceptance criteria should be used for routine QC testing of venetoclax tablets.

USP Apparatus	Dips per min	Medium/ Volume/Temperature	Acceptance Criteria
3	20 ± 5%	250 mL of 50 mM sodium phosphate buffer, pH 6.8 ± 0.05 with 0.4% sodium dodecyl sulfate (SDS) and 3 small drops of antifoaming agent per vessel at 37 ± 0.5°C	10 mg: Q = (b) (4)% in 1.5 h Q = (b) (4)% in 2 h 50 mg: Q = (b) (4)% in 2 h Q = (b) (4)% in 3 h 100 mg: Q = (b) (4)% in 3 h Q = (b) (4)% in 4 h

E. Novel Approaches NA

F. Any Special Product Quality Labeling Recommendations NA

G. Life Cycle Knowledge Information (see Attachment A) NA



**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE
SUMMARY**

Application Technical Lead Signature: Tracey Rogers, PhD 04-Apr-16

NDA 208573 is recommended for approval

145 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics review of the NDA is focused on the evaluation of (1) the proposed dissolution acceptance criteria, and (2) the adequacy of the bridging between the pivotal clinical trial and the proposed commercial formulations.

Venetoclax oral tablets are immediate release tablets intended for once daily administration. Venetoclax is a poorly water-soluble compound, formulated (b) (4)

. The three tablet strengths (10 mg, 50 mg, 100 mg) of venetoclax tablets are (b) (4)

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The proposed *in vitro* dissolution method and acceptance criteria for the routine QC testing of venetoclax tablets are summarized in Table 38-1 and Table 38-2, respectively.

Table 38-1. *In Vitro* Dissolution Method for QC Testing of Venetoclax Tablets

Parameter	Condition
Apparatus	Apparatus 3 (with syringe pump, filter changer and fraction collector)
Vessels	6 rows x 300 mL
Dips Per Minute	20 ± 5%
Medium	250 mL of 50 mM sodium phosphate buffer, pH 6.8 ± 0.05 with 0.4% sodium dodecyl sulfate (SDS) and 3 small drops of antifoaming agent per vessel at 37 ± 0.5°C
Sampling Time Points (proposed for QC)	10 mg Tablets: (b) (4) 1.5 and 2 hours 50 mg Tablets: 2 and 3 hours 100 mg Tablets: (b) (4) and 4 hours
Bottom Screen	200 mesh stainless steel
Assay	HPLC

Per 3.2.P.5.2 Dissolution of Venetoclax Tablets (RTM.C5646): (b) (4)
(b) (4)

Table 38-2. Proposed Dissolution Acceptance Criteria for Venetoclax Tables

Dosage Strength	Time Point	Acceptance Criteria ^a
10 mg	(b) (4)	(b) (4)
	1.5 Hour	
	2.0 Hour	
50 mg	(b) (4)	(b) (4)
	2.0 Hour	
	3.0 Hour	
100 mg	(b) (4)	(b) (4)
	(b) (4)	
	4.0 Hour	

NMT = not more than; LA = labelled amount; NLT = not less than
(b) (4)

Per the Applicant, the proposed criterion corresponds to not less than (NLT) the overall mean % released observed for clinical study batches, minus approximately (b) (4)%. The criterion for the final specification time point is the first time point where the overall

mean of tablets studied in the clinic is greater than (b) (4) % Released. Because of the limited dissolution data for the 10 mg strength, the data from the lots manufactured by the proposed commercial site were also considered. The Applicant reported that the dissolution profile does not change during the shelf life of the product as indicated by the primary and site-specific stability data.

Reviewer's Assessment:

Dissolution Method

Previously, the Biopharmaceutics reviewer of IND 11059 (SDN-208) had determined that the Applicant's proposed dissolution method is adequate for routine QC testing of venetoclax tablets, based on the method's capability to discriminate changes in (b) (4) drug substance content and (b) (4) of the tablets. Additionally, due to the observed (b) (4) dissolution of the tablets, the Biopharmaceutics reviewer recommended using a multi-point dissolution acceptance criteria. Note that the (b) (4)

The validation data (e.g., robustness with respect to dissolution media pH, antifoaming agent level, buffer salts and surfactant concentrations; equivalence of alternative filters; sampling type) for the dissolution method are satisfactory.

Dissolution Acceptance Criteria

(b) (4)

	f ₂
10 mg vs 50 mg	(b) (4)
10 mg vs 100 mg	
50 mg vs 100 mg	

Table 38-3. Characteristics of the three strengths of film-coated venetoclax tablets

Parameter	10 mg (pale yellow)	50 mg (beige)	100 mg (pale yellow)
Shape	Round, biconvex	oblong, biconvex	oblong, biconvex
Diameter (mm)	6	14 x 8	17.2 x 9.5
core weight (mg)	(b) (4)		
Thickness (mm)			
mean hardness/crushing strength (N)			

This Reviewer considers the Applicant's proposal to use a strength-dependent dissolution specification for venetoclax tablets to be acceptable. (b) (4)

(b) (4). The Reviewer recommends a simpler strength dependent two-point dissolution acceptance criteria that is based on varying the specification time points to achieve fixed dissolution levels, and interpreted using USP Acceptance Table 1 (for immediate release dosage forms). Refer to Table 38-4 for the summary of the Reviewer's analyses of all the lots with dissolution data generated using the proposed dissolution method. Using the Reviewer's recommended acceptance criteria, all the clinical trial batches and the proposed commercial batches passed USP Stage 2 dissolution testing. One lot each of the 50 mg and 100 mg tablets included in the stability program did not initially meet the minimum cut-off at the recommended second/final specification timepoint (b) (4); both lots eventually passed USP Stage 3 testing.

Table 38-4. Cumulative Drug Released from Clinical Trial Batches, Proposed Commercial Batches, and Stability Batches

	Q	Timepoint (h)	Pivotal/Supportive Clinical Trial Batches (at release)		Proposed Commercial Batches (at release)		Stability Batches (Months 0 to 12 of Long-Term Storage)	
			n	Mean (%CV) [Range]	n	Mean (%CV) [Range]	n*	Mean (%CV) [Range]
10 mg	(b) (4)	1.5						
		2						
50 mg	(b) (4)	2						
		3						
100 mg	(b) (4)	3						
		4						

The following Information Request was sent to the Applicant on 2/9/2016:

Based on our review of dissolution profiles from the pivotal and supportive clinical trials and the proposed commercial batches at the time of release and/or during stability testing, we recommend the following dissolution acceptance criteria for venetoclax tablets. Submit the revised drug product specification table with the recommended changes to the dissolution acceptance criteria as an amendment to the NDA.

Tablet Strength	Specification Timepoint	
	When Q = $\frac{(b)}{(4)}\%$ of labeled amount	When Q = $\frac{(b)}{(4)}\%$ of labeled amount
10 mg	1.5 h	2 h
50 mg	2 h	3 h
100 mg	3 h	4 h

*Evaluated per USP <711> Acceptance Table 1

On 3/1/2016, the Applicant accepted the FDA recommended dissolution acceptance criteria, and updated the Drug Product Specification table accordingly. Based on the updated stability data provided by the Applicant in response to the Drug Product Reviewer's Information Request, all the final packaging lots (10 mg, 50 mg, and 100 mg) produced at the proposed commercial manufacturing site (Sligo, Ireland) conformed to the FDA recommended dissolution acceptance criteria after USP Stage 1 dissolution testing at the latest long-term stability timepoint (Month 12, 30°C/75% RH).

(b) (4)

(b) (4)

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Yes, there is adequate bridging between the drug product used during clinical development and the proposed commercial product.

(b) (4)

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS****Reviewer's Recommendation and Signature:**

From a Biopharmaceutics perspective, NDA 208-573 for venetoclax tablets is recommended for APPROVAL.

3/1/2016

Gerlie Gieser, Ph.D.

Biopharmaceutics Reviewer

Division of Biopharmaceutics/OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Gieser's review and approval recommendation for NDA 208573.

3/2/2016

Okpo Eradiri, Ph.D.

Acting Biopharmaceutics Lead

Division of Biopharmaceutics/OPQ

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

See Process

Reviewer's Assessment: See Process

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

N/A

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The proposed manufacturing process and controls assure acceptable microbial quality of the final drug product.

03/11/2016

Pete Guerrieri, Ph.D.

Process and Micro Reviewer

Office of Process & Facilities/OPQ

Secondary Review Comments and Concurrence:

I concur with the assessment by Pete Guerrieri.

Jennifer Maguire, Ph.D.

Acting Branch Chief, OPQ/OPF/DPA I/Branch 2

March 18, 2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?

Abbvie requested for a categorical exclusion from the requirement to prepare an environmental assessment (EA) under 21 CFR § 25.31(b) for the active pharmaceutical ingredient (API), venetoclax.

45. Is the applicant's Environmental Assessment adequate for approval of the application?

To the applicant's knowledge, no extraordinary circumstances exist for the API that would warrant the preparation of an EA.

Reviewer's Assessment:

No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant and/or animal material 21 CFR 25.21(b). **Granted.**

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL**Reviewer's Assessment and Signature:**

Acceptable

Rajiv Agarwal 1-MAR-2016

Secondary Review Comments and Concurrence:

I concur.

Anamitro Banerjee, Ph.D.

Acting Branch Chief, OPQ/ONDP/DNDP I/Branch 2

March 17, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For ANDA only

A. Labeling & Package Insert

a) DESCRIPTION section

- i) Is the information accurate? Yes No

If "No," explain.

- ii) Is the drug product subject of a USP monograph? Yes No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

Reviewer's Assessment:

b) HOW SUPPLIED section

- i) Is the information accurate? Yes No

If "No," explain.

- ii) Are the storage conditions acceptable? Yes No

If "No," explain.

Reviewer's Assessment:

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Yes No N/A

If "No," explain.

Reviewer's Assessment:

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? Yes No
If "No," explain.

Reviewer's Assessment:

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Reviewer's Assessment:

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Yes	Adequate
Dosage form, route of administration	Yes	Adequate
Controlled drug substance symbol (if applicable)	Not applicable	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Yes	Adequate

Conclusion: Adequate per 21 CFR 201.57 (a) (2).

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Table 4. TRADENAME Tablet Strength and Description

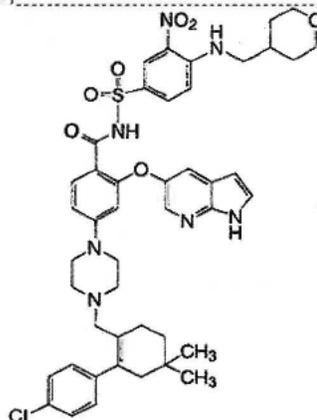
Tablet Strength	Description of Tablet
10 mg	Round, biconvex shaped, pale yellow film-coated tablet debossed with "V" on one side and "10" on the other side
50 mg	Oblong, biconvex shaped, beige film-coated tablet debossed with "V" on one side and "50" on the other side
Tablet Strength	Description of Tablet
	side
100 mg	Oblong, biconvex shaped, pale yellow film-coated tablet debossed with "V" on one side and "100" on the other side

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	10, 50 and 100 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided	Adequate

Conclusion: Adequate per 21 CFR 201.57 (a) (4).

#11: Description (21CFR 201.57(c)(12))**[11 DESCRIPTION]**

Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{59}ClN_7O_5S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. Venetoclax is described chemically as 4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide) and has the following chemical structure:



[TRADENAME] tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated

tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol and titanium dioxide. Each tablet is debossed with "V" on one side and "10", "50" or "100" corresponding to the tablet strength on the other side.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Yes	Adequate
Dosage form and route of administration	Yes	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Yes	Adequate
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	Yes	Adequate
Chemical name, structural formula, molecular weight	Yes	Adequate
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Low aqueous solubility	Adequate

Conclusion: Conclusion: Adequate per 21 CFR 201.57 (a) (12).

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

[6 HOW SUPPLIED/STORAGE AND HANDLING].....

TRADENAME is dispensed as follows:

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
Starting Pack	Each pack contains four weekly wallet blister packs: <ul style="list-style-type: none"> • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets) 	0074-0579-28
10 mg Wallet	14 x 10 mg tablets	0074-0561-14
50 mg Wallet	7 x 50 mg tablets	0074-0566-07
10 mg Unit Dose	2 x 10 mg tablets	0074-0561-11
50 mg Unit Dose	1 x 50 mg tablet	0074-0566-11
100 mg Unit Dose	1 x 100 mg tablet	0074-0576-11
100 mg Bottle	120 x 100 mg tablets	0074-0576-22

TRADENAME 10 mg film-coated tablets are round, biconvex shaped, pale yellow debossed with "V" on one side and "10" on the other side.

TRADENAME 50 mg film-coated tablets are oblong, biconvex shaped, beige debossed with "V" on one side and "50" on the other side.

TRADENAME 100 mg film-coated tablets are oblong, biconvex shaped, pale yellow tablet debossed with "V" on one side and "100" on the other side.

Store at or below 86°F (30°C).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Yes	Adequate
Available units (e.g., bottles of 100 tablets)	Yes	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	Adequate
Special handling (e.g., protect from light, do not freeze)	Not applicable	
Storage conditions	Yes	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured and Marketed by:
AbbVie Inc.
North Chicago, IL 60064

and

Marketed by:
Genentech Inc.
South San Francisco, CA 94080

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Yes	Adequate

Conclusion: Adequate

2. Container and Carton Labeling**1) Immediate Container Label**

(b) (4)

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Venclexta (venetoclax)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Adequate
Route of administration (21.CFR 201.100(b)(3))	Provided	Adequate
Net contents* (21 CFR 201.51(a))	Provided	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not applicable	Adequate
Lot number per 21 CFR 201.18	Provided	Adequate
Expiration date per 21 CFR 201.17	Provided	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Others	Caution statement: Keep out of reach of children	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

AbbVie accepts the recommendations to amend the labeling on the primary and secondary container closure labels and provides the color mock ups via amendment dated 29-MAR-2016. Several packaging configuration are listed in the application.

(b) (4)

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Venclexta (venetoclax)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Provided	Adequate
Net contents (21 CFR 201.51(a))	Provided	Adequate
Lot number per 21 CFR 201.18	Provided	Adequate
Expiration date per 21 CFR 201.17	Provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not applicable	
Sterility Information (if applicable)	Not applicable	Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
“See package insert for dosage information” (21 CFR 201.55)	Provided	Adequate
“Keep out of reach of children” (optional for Rx, required for OTC)	Provided	Adequate
Route of Administration (not	Not applicable	

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		
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Conclusion:

Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING**Reviewer's Assessment and Signature:**

The information contains in PI and primary and secondary container closure labels is adequate.

Rajiv Agarwal
31-MAR-2016

Secondary Review Comments and Concurrence:

I concur with Dr. Rajiv Agarwal's assessment.

Anamitro Banerjee, Ph.D.
Acting Branch Chief, OPQ/ONDP/DNDP I/Branch 2
April 04, 2016

II. List of Deficiencies To Be Communicated

Drug Substance

Drug Product

Process

Facility

Biopharmaceutics

Microbiology - None

Environmental

Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	L	Factors identified in the application will not affect the assay or stability	Acceptable	(b) (4)
					Changes in formulation or process should be assessed according to relevant SUPAC
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	L	Factors identified in the application will not affect the physical stability	Acceptable	(b) (4)
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	L	Assessed during development	Acceptable	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> • Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site 	L	Assessed during development	Acceptable	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REPORT SUMMARY

TO: Rajiv Agarwal, CMC Reviewer
Tracey Rogers, CMC Lead
Monica Cooper, CMC Reviewer
Anamitro Banerjee, Branch Chief (Acting)
Rabiya Laiq, Methods Validation Project Manager
E-mail Address: rajiv.agarwal@fda.hhs.gov
Phone: 301-796-1322

FROM: FDA
Division of Pharmaceutical Analysis
Laura C. Pogue, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: David Keire, Ph.D., Lab Chief, Branch I
Phone: (314) 539-3850

SUBJECT: Methods Verification Report Summary

Application Number: NDA 208573

Name of Product: Venetoclax Tablets 10mg, 50mg, 100mg

Applicant: AbbVie Inc.

Applicant's Contact Person: Tuah Jenta Ph.D, RAC Associate Director Regulatory Affairs

Address: 1 N. Waukegan Road. Dept. PA77/Bldg AP30 North Chicago, IL 60064

Telephone: 847-937-2434

Email: tuah.jenta@abbvie.com

Date Methods Verification Consult Request Form Received by DPA: 1/7/2016

Date Methods Verification Package Received by DPA: 1/15/2016

Date Samples Received by DPA: 1/15/2016

Date Analytical Completed by DPA: 2/23/2016

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



Date: February 23, 2016

To: Rajiv Agarwal, CMC Reviewer
Tracey Rogers, CMC Lead
Monica Cooper, CMC Reviewer
Anamitro Banerjee, Branch Chief (Acting)
Rabiya Laiq, Methods Validation Project Manager

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA

Through: David Keire, Ph.D., Acting Lab Chief, Branch II, CDER/OPQ/OTR/DPA

Subject: Method Verification of NDA 208573: Venetoclax film coated tablet (10mg, 50mg and 100 mg)

The following methods were verified and found acceptable for quality control and regulatory purposes:

- 1) 3.2.S.4.2 Analytical Procedure for Assay of Venetoclax by HPLC (RTM. 5319, page 1-4).
- 2) 3.2.S.4.2 Analytical Procedure for Impurities of Venetoclax by HPLC (RTM. 5320, page 1-5).
- 3) 3.2.P.5.2 Analytical Method for Assay and Identification of Venetoclax tablets: 10 mg, 50 mg and 100mg by HPLC (RTM. C5477 page 1-5).
- 4) 3.2.P.5.2A Analytical Method for Degradation Products of of Venetoclax tablets: 10 mg, 50 mg and 100mg by HPLC (RTM. C5512, page 1-4).

Analyst worksheets can be viewed through ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c862a1>

Summary of Analysis:

1) 3.2.S.4.2 Analytical Procedure for Assay of Venetoclax by HPLC (RTM. 5319, page 1-4).

Assay:

	% Assay (w/w).	Acceptance Criteria
DS Sample -1	(b) (4)	(b) (4)
DS Sample -2	(b) (4)	(b) (4)
DS Sample -3	(b) (4)	(b) (4)
Average	(b) (4)	(b) (4)

Identification by RT: The retention time of the venetoclax in sample solution was the same as venetoclax standard injection, RT = (b) (4), PASS.

2) 3.2.S.4.2 Analytical Procedure for Impurities of Venetoclax by HPLC (RTM. 5320, page 1-5).

RRT	Impurity	Average (3) % Relative Substance	Limits
(b) (4)			

3) 3.2. P.5.2 Analytical Method for Assay and Identification of Venetoclax tablets: 10 mg, 50 mg and 100mg by HPLC (RTM. C5477 page 1-5).

Assay:

Strength	10 mg	50 mg	100 mg
	% Label Amount	% Label Amount	% Label Amount
Average (2)	(b) (4)		
Limit within (b) (4) % - (b) (4) %	Pass	Pass	Pass

Identification by RT:

Strength	10 mg	50 mg	100 mg
Average % RT Agreement	(b) (4)		
Limit: within (b) (4) % - (b) (4) %	Pass	Pass	Pass

Identification by UV: The UV spectra of venetoclax obtained from the sample preparations (10 mg, 50 mg and 100 mg) are identical to the UV spectrum of venetoclax obtain from the standard preparation in the range of (b) (4) to (b) (4) with respect to their maxima.

4) 3.2.P.5.2A Analytical Method for Degradation Products of of Venetoclax tablets: 10 mg, 50 mg and 100mg by HPLC (RTM. C5512, page 1-4).

10 mg	Average		
RRT	% Degradant	Compound name	Limits
(b) (4)			

50 mg	Average		
RRT	% Degradant	Compound name	Limits
(b) (4)			

100 mg	Average		
RRT	% Degradant	Compound name	Limits
(b) (4)			

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/s/

LAURA POGUE
02/24/2016

DAVID A KEIRE
02/24/2016