CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210563Orig1s000
210563Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210563
Review #1

Drug Name/Dosage Form	Imbruvica® (Ibrutinib) Tablets
Strength	140 mg, 280 mg, 420
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pharmacyclics LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission (SD 1)	31-Aug-17	All
Amendment (SD 2)	21-Sept-17	DP
Amendment (SD 4)	20-Oct-17	DP, Biopharm
Amendment (SD 5)	3-Nov-17	DP
Amendment (SD 8)	8-Dec-17	Process
Amendment (SD 9)	18-Dec-17	Process
Amendment (SD 11)	19-Dec-17	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sherita McLamore	n/a
Drug Product	Xing Wang	Anamitro Banerjee
Process	Quamrul Majumder	Ying Zhang
Microbiology	n/a	n/a
Facility	Ziyang Su	Ruth Moore
Biopharmaceutics	Om Anand	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Environmental	Xing Wang	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205552	Manufacture and control of Drug Substance
IND	102688	Drug development

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL** of NDA 210563 for IMBRUVICA® (ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg. As part of this action, OPQ grants a 24-month expiration period for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). The Office of Pharmaceutical Quality has no Post-Marketing Commitments (PMCs) or Post-Marketing Requirements (PMRCs) to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 210563 was submitted for IMBRUVICA® (ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Ibrutinib is an orally bioavailable, small molecule, Bruton tyrosine kinase inhibitor (BTK). Imbruvica (Ibrutinib) originally investigated under IND 102,688 and approved under NDA 205552 (November 2013) as a 140 mg capsule for a variety of B-cell malignancies including:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- CLL/SLL with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

The drug product, IMBRUVICA® (ibrutinib) tablets for oral use was designed to be a new, smaller tablet formulation of the approved product which offers a single tablet alternative to patients and reduces pill burden. Ibrutinib was granted breakthrough designation in 2013 and has orphan designation.

The ibrutinib drug substance used in the manufacture of IMBRUVICA® (ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, and 560 mg is identical to that which is used for the approved 140 mg ibrutinib capsules. The drug substance is a non-hygroscopic, small, chiral molecule that is manufactured (b) (4). The applicant references NDA 205552 for all aspects of manufacture and control of the drug substance. The drug product is presented as a 140 mg, 280 mg, 420 mg, and 560 mg immediate release, film-coated tablets containing the active together with compendial, commonly used excipients. All four strengths are (b) (4)

(b) (4) similar. They are easily differentiated by size, debossing, shape and/or color.

The recommended dosing regimen of IMBRUVICA® Tablets for MCL and MZL is 560 mg orally once daily until disease progression or unacceptable toxicity. The recommended dosing regimen for IMBRUVICA® Tablets for CLL/SLL and WM is 420 mg orally once daily until disease progression or unacceptable toxicity. The recommended dosing regimen for IMBRUVICA® Tablets for CLL/SLL when used in combination with bendamustine and rituximab (administered every 28 days for up to 6 cycles) is 420 mg orally once daily until disease progression or unacceptable toxicity. The recommended dosing regimen of IMBRUVICA for cGVHD is 420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 210563 and grants a 24-month expiration period for the drug product when stored at ICH controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	• Mantle cell lymphoma (MCL) who have received at least one prior therapy • Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) • CLL/SLL with 17p deletion • Waldenström's macroglobulinemia (WM) • Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy • Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	MDD is 420 mg for CLL/SLL, WM and cGVHD and 560 mg for MCL and MZL
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Ibrutinib drug substance is a white to off-white, non-hygroscopic, highly-crystalline solid that is practically insoluble in water and is freely soluble in DMF, THF, DCM and DMSO. Ibrutinib drug substance is small chiral molecule that is manufactured (b) (4) (b) (4) (b) (4) The applicant references NDA 205552 for all aspects of manufacture and control of ibrutinib drug substance. NDA 205552 was submitted to the agency in April

of 2013 and approved in November of that same year. The application is recommended for approval from the drug substance perspective.

Drug Product

The drug product is presented as 140 mg, 280 mg, 420 mg, and 560 mg film-coated, immediate release tablets. All four strengths are manufactured (b) (4) and are differentiated by color, shape, size, and debossing. The 140 mg tablet is presented as a (b) (4) round yellow-green tablet debossed on one side with "ibr" and "140" on the other side. The 280 mg tablet is presented as a (b) (4) oblong, purple tablet debossed on one side with "ibr" and "280" on the other side. . The 420 mg tablet is presented as a (b) (4) oblong yellow-green to green tablet debossed on one side with "ibr" and "420" on the other side. The 560 mg tablet is presented as a (b) (4) oblong yellow to orange tablet debossed on one side with "ibr" and "560" on the other side. The tablet core formulation includes USP/NF grade lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate. (b) (4) (b) (4) (b) (4) The drug product formulation contains no novel excipient. All excipients are compendial and commonly used in solid oral dosage forms.

The drug product is manufactured controlled, packaged, and release tested by Catalent CTS, LLC or by AbbVIe Inc at a commercial batch size of (b) (4) tablet which corresponds to (b) (4) for the 140, 280, 420 and 560 mg tablets, respectively. IMBRUVICA® (ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg will be packaged in (b) (4) blisters with push-through aluminum lidding foil. The secondary packaging for the blister cards is a (b) (4) carton. The blister packaging was chosen based on the ability to provide adequate protection for the drug product from moisture and light throughout its shelf life.

The drug product specifications are consistent with ICH Q6A and provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 24 month expiry, the applicant provided 12 months of primary stability data for ten registration batches of the drug product: 3 batches each of 560 mg, 420 mg and 140 mg strength and 1 batch of 280 mg strength. All batches used in the primary stability study were manufactured with the commercial formulation, at scale using the proposed commercial process and were manufactured at proposed commercial sites. All batches were packaged in the proposed commercial container closure systems. The stability protocol included a bracket (i.e. one batch of the 280 mg table). As all potencies were manufactured from (b) (4) the bracket was in accordance with ICH Q1D and therefore acceptable. In addition to the primary stability data, the applicant provided supportive stability data for clinical tablet batches (see drug product review for details of supportive data).

The stability studies were executed in accordance with the ICH 1A and Q1B. The available stability data shows consistency over time and the statistical analysis of the long term data support the proposed expiry. Based on the 12 months of stability data included in this application, Pharmacyclics, LLC. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored between 20°C and 25ºC (with excursions permitted from between 15°C to 30ºC).

The application is recommended for approval from the drug product perspective.

Process

The drug product is manufactured, packaged and release tested by AbbVie Inc. of IL and Catalent CTS, LLC of MO commercial batch size of (b) (4) tablet which corresponds to (b) (4) for the 140, 280, 420 and 560 mg tablets, respectively. The drug product is manufactured (b) (4)

(b) (4)

The proposed process parameters and (b) (4) controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate (b) (4) controls and operating parameters. The application is recommended for approval from a manufacturing process perspective.

Biopharmaceutics

Ibrutinib is a BCS Class II drug. The biopharmaceutics review of this application focused on the acceptability of the proposed dissolution method and acceptance criterion for the routine quality control (QC) testing of the proposed drug product at batch release and on stability; the biowaiver request for the intermediate strengths (280 and 420) and the bridging between the proposed commercial product and the product used in the clinical studies.

The dissolution method for the 140 and 280 mg strengths included a USP Apparatus II (Paddle) at 75 rpm in 900 mL of 3.0% *w/v* Tween 20 in 0.05 M potassium phosphate buffer, pH 6.8@37.0± 0.5° C. The dissolution method for the 420 and 560 mg strengths included a USP Apparatus II (Paddle) at 75 rpm in 900 mL of 6.0% *w/v* Tween 20 in 0.05 M potassium phosphate buffer, pH 6.8@37.0± 0.5° C. It was concluded that the proposed *in-vitro* dissolution test is adequate for quality control as applicant has adequately studied the discriminating ability of the proposed dissolution method. Thus the dissolution methods and acceptance criterion of Q (b) (4) % at 45 min for all four strengths is acceptable.

With regards to the biowaiver and the bridging, it was concluded that the applicant provided adequate data to support the biowaiver request for intermediate strengths (280 mg and 420 mg) and that the and that the bridging between the proposed commercial product and the product used in the clinical studies is acceptable. Accordingly, the biowaiver request was granted and this application is recommended for approval from a biopharmaceuticals perspective.

Facilities:

NDA 210563 included a total of ten (10) sites:

(b) (4)

- AbbVie Inc. (FEI 3009751352): This site was responsible for the manufacture, packaging and labeling of final drug product. This site had a high initial risk assessment and a final recommendation of acceptable.

- Catalent CTS, LLC (FEI 3002929455): This site was responsible for the manufacture, release and stability testing of final drug product and release and stability testing of the drug substance. This site had a low initial risk assessment and a final recommendation of acceptable.

- AbbVie Inc. (FEI 1411365): This site was responsible for release and stability testing of final drug product. This site had a low to medium initial risk assessment and a final recommendation of acceptable.

Following a review of this application and inspectional documents, it was concluded that there were no manufacturing risks that preclude approval of this application. Based on the firm's inspectional history, EIR reviews and District Office (DO) recommendations, each of the manufacturing facilities included in NDA 210563 are acceptable and the Overall Manufacturing Inspection Recommendation for this NDA is approval.

Environmental Assessment

The applicant requested a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.15(d) and 21 CFR 25.31(b) based on the calculation of the expected introduction concentration (EIC) value for ibrutinib into the aquatic environment. The EIC was determined to be 0.225 ppb.

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

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ENVIRONMENTAL ANALYSIS

Imbruvica® (ibrutinib) capsules 140 mg has been commercially available in the United States since November 2013 (NDA 205552). Pharmacyclics was granted a categorical exclusion (under 21 CFR 25.31(b)) from the preparation of an environmental assessment of ibrutinib based on estimated concentration of less than 1 part per billion (ppb) of drug substance entering the aquatic environment at the point of entry (EIC-Aquatic).

Pharmacyclics has developed a new tablet dosage form in four different strengths (140 mg, 280 mg, 420 mg, and 560 mg). The new tablet dosage form is intended to be marketed for use in the same approved indications and at the same recommended dose level as the currently approved ibrutinib capsules. Therefore, no change is anticipated in the estimated quantity of the drug substance to be produced for direct use in any of the next five years. The quantity of drug substance to be used in all dosage forms and strengths will remain the same as presented in Section 1.12.14 Environmental Analysis of the approved NDA 205552. Justification for the categorical exclusion from environmental assessment of ibrutinib was presented in NDA 205552 and is applicable to the current submission as well. A cross-reference to the Section 1.12.14 Environmental Analysis of the approved NDA 205552 is provided.

Reviewer's Assessment: Adequate
Per NDA 205552, for ibrutinib, EIC-Aquatic = 0.225 ppb < 1 ppb. The EA statement is adequate.

Primary EA Reviewer Name and Date: Xing Wang, Ph.D., ONDP/DNDPI/NDPBII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D., Acting Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

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Anamitro Banerjee

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Date: 1/04/2018 10:54:16PM
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CHAPTER IV: Labeling

Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.5, 1.6)	08/2017
Dosage and Administration (2.2, 2.3, 2.4)	XX/XXXX
Warnings and Precautions (5)	01/2017

----------INDICATIONS AND USAGE----------

IMBRUVICA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).
  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (1.5).
  Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (1.6).

----------DOSAGE AND ADMINISTRATION----------

- MCL and MZL: 560 mg taken orally once daily (2.2).
- CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily (2.2).

(b) (4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsule: 140 mg (3)
Tablet: 140 mg, 280 mg, 420 mg, 560 mg (3) (REFERENCE H1)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hemorrhage: Monitor for bleeding and manage (5.1).
- Infections: Monitor patients for fever and infections, evaluate promptly, and treat (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).

(b) (4)

- Hypertension: Monitor blood pressure and treat (5.5).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.6).
- Tumor Lysis Syndrome (TLS): Assess baseline risk and take precautions. Monitor and treat for TLS (5.7).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug and for 1 month after cessation of therapy. Advise men to avoid fathering a child during the same time period (5.8, 8.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia (6).

The most common adverse reactions (≥20%) in patients with cGVHD were fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacyclics at 1-877-877-3536 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A Inhibitors: Dose adjustments may be recommended (2.4, 7.1).
- CYP3A Inducers: Avoid coadministration with strong CYP3A inducers (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA in patients with (b) (4) severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA dose (2.5, 8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: XX/XXXX

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	IMBRUVICA® (ibrutinib)	Adequate
Dosage form, route of administration	Capsules, for oral use Tablets, for oral use	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Capsule: 140 mg Tablet: 140 mg, 280 mg, 420 mg and 560 mg	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

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

140 mg capsules

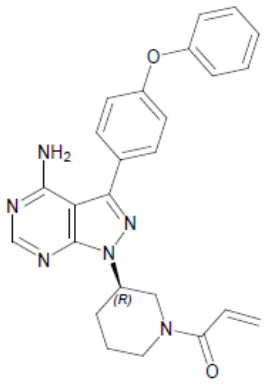
Tablets: 140 mg, 280 mg, 420 mg, and 560 mg

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Capsule, tablet	Adequate
Strengths: in metric system	See above	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided (b) (4)	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



IMBRUVICA (ibrutinib) is available as immediate-release oral capsules and immediate-release oral tablets.

IMBRUVICA (ibrutinib) capsules for oral administration are (b) (4) (b) (4) Each capsule (b) (4) contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. (b) (4) (b) (4)

IMBRUVICA (ibrutinib) tablets for oral administration are available in the following dosage strengths: 140 mg, 280 mg, 420 mg, and 560 mg. Each tablet contains ibrutinib (active

ingredient) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The film coating for each tablet contains ferrosoferric oxide (140 mg, 280 mg, and 420 mg tablets), polyvinyl alcohol, polyethylene glycol, red iron oxide (280 mg and 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg, and 560 mg tablets).

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	IMBRUVICA (ibrutinib)	Adequate
Dosage form and route of administration	Capsule, tablets	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Free base, not salt	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)		N/A
Pharmacological/ therapeutic class	Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK)	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion: Adequate

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

The white opaque 140 mg capsules marked with "ibr 140 mg" in black ink are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle: NDC 57962-140-09

- 120 capsules per bottle: NDC 57962-140-12

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.

The IMBRUVICA (ibrutinib) tablets are supplied in 4 strengths in the following packaging configurations:

• 140 mg tablets: Yellow green to green round tablets debossed with “ibr” on one side and “140” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-014-28

• 280 mg tablets: Purple oblong tablets debossed with “ibr” on one side and “280” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-280-28

• 420 mg tablets: Yellow green to green oblong tablets debossed with “ibr” on one side and “420” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-420-28

• 560 mg tablets: Yellow to orange oblong tablets debossed with “ibr” on one side and “560” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-560-28

Store tablets in original packaging at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).

Item	Information Provided in NDA	Reviewer’s Assessment
Strength of dosage form	Capsule 140 mg Tablets: 140 mg, 280 mg, 420 mg and 560 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Capsules: bottles of 90; bottles of 120 Tablets: Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store tablets in original packaging at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).	Adequate

Conclusion: Adequate

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

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

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

Conclusion: Adequate

Carton Labeling

(b) (4)

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tem	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Imbruvica® (ibrutinib) tablets	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	140 mg, 280 mg, 420 mg, 560 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	Take IMRUVICA tablet by mouth	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)**	"See accompanying literature for dosage information" (PI inserted in the carton)	Adequate
Lot number per 21 CFR 201.18	Reserved space	Adequate
Expiration date per 21 CFR 201.17	Reserved space	Adequate
"Rx only" statement per 21 CFR	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		Adequate

Reviewer's Assessment: Adequate

List of Deficiencies: None

Primary Drug Product Reviewer Name and Date:

Xing Wang, Ph.D., ONDP/DNDPI/NDPBII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D., Acting Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

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Anamitro Banerjee

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BIOPHARMACEUTICS REVIEW	
Application No.	NDA 210563-ORIG-1
Type of Submission	505(b)(1)/New dosage form and new strengths
Applicant/Sponsor	Pharmacyclics LLC
Product Name	Imbruvica® (Ibrutinib) Tablets
Dosage Form/Strength	Immediate Release Tablets, 140 mg, 280 mg, 420 mg, 560 mg
Route of Administration	Oral
Intended Use	Treatment of lymphoma, leukemia and chronic graft versus host disease
Submission Date	08/31/2017 (Original Submission) 10/20/2017 (Quality Amendment Response to IR)
Primary Reviewer	Om Anand, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.

1. EXECUTIVE SUMMARY

Background: NDA 210563 for Imbruvica® (Ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg is a 505(b)(1) submission. Ibrutinib is a first-in-class, orally administered, potent small-molecule, and inhibitor of Bruton's tyrosine kinase (BTK), a mediator of critical B-cell signaling pathways implicated in the pathogenesis of B-cell cancers. Previously, Imbruvica® (Ibrutinib) capsules have been approved in NDA205552 which are available in only 140 mg strength. The recommended adult dose for ibrutinib is 560 mg (4x140 mg capsules once daily) for patients with MCL and 420 mg (3x140 mg capsules once daily) for patients with chronic lymphocytic leukemia (CLL) or Waldenstrom's macroglobulinemia (WM). Pharmacyclics has developed new [redacted] (b) (4) filmcoated tablet formulation of ibrutinib (in 140 mg, 280 mg, 420 mg, and 560 mg strengths) which is the subject of the Review of this NDA.

Review Summary: The Biopharmaceutics review is focused on the evaluation of the data supporting the proposed dissolution method and acceptance criterion, biowaiver request and the bridging between the proposed commercial product and the product used in the clinical studies.

Dissolution method: ACCEPTABLE

The following proposed dissolution methods are acceptable:

Apparatus	Speed	Volume	Medium
For 140 and 280 mg strengths			
USP 2 (paddle)	75 rpm	900 mL	3.0% *w/v* Tween 20 in 0.05 M potassium phosphate buffer, pH 6.8@37.0± 0.5° C
For 420 and 560 mg strengths			
USP 2 (paddle)	75 rpm	900 mL	6.0% *w/v* Tween 20 in 0.05 M potassium phosphate buffer, pH 6.8@37.0± 0.5° C

Dissolution Acceptance Criterion: ACCEPTABLE

The dissolution acceptance criterion of Q= (b) (4)% at 45 minutes for all strengths of Ibrutinib Tablets is acceptable.

Biowaiver Request: ACCEPTABLE

The Applicant's biowaiver request for intermediate strengths (280 mg and 420 mg) is granted.

Bridging: ACCEPTABLE

The bridging between the proposed commercial product and the product used in the clinical studies is acceptable.

Discriminating ability of the dissolution method:

The Applicant has adequately studied the discriminating ability of the proposed dissolution method**.** The dissolution method can clearly discriminate the formulations manufactured using (b) (4) drug substance, (b) (4). The dissolution method can also pick up the changes occurring in the release profile of Ibrutinib Tablets during stress conditions (40° C/75% RH). Though there is no clear discrimination, there is a rank order in the dissolution profiles of Ibrutinib Tablets (b) (4). The method is not discriminating with regard to minor formulation changes.

Recommendation:

From a Biopharmaceutics perspective, NDA 210563 for Imbruvica® (Ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg is recommended for **APPROVAL**

2. List of submissions reviewed:

eCTD sequence #	Received date	Document
0001	08/31/2017	Original NDA submission
0014	10/20/2017	Quality/Response to Quality/Biopharmaceutics Information Request

3. Highlight Key Outstanding Issues from Last Cycle: None

4. Concise Description Outstanding Issues Remaining: None

5. BCS designation:

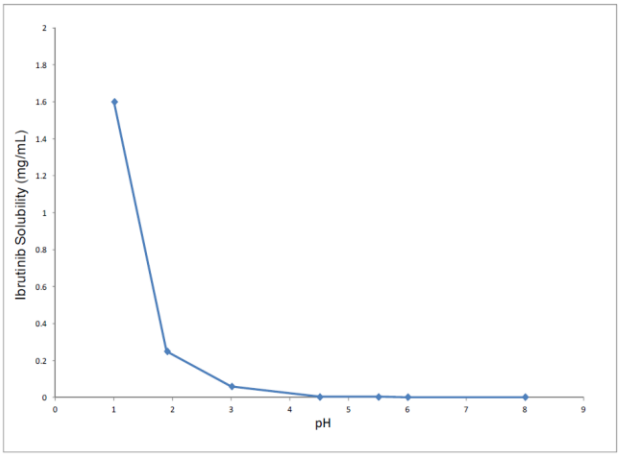
As per the Applicant, Ibrutinib is a Biopharmaceutical Classification System (BCS) Class 2 compound (low solubility/high permeability) and is practically insoluble to slightly soluble in water and aqueous buffered solutions. In a human-derived Caco 2 model the in-vitro permeability of ibrutinib was determined to be high (apparent permeability [A to B] = 57.9 × 10^{-6} cm/s, efflux ratio = 0.13. In addition, the extent of absorption in humans for ibrutinib was determined to be ≥ 90%, demonstrating high permeability (refer Ibrutinib capsule NDA 205552).

The solubility values obtained for ibrutinib in various aqueous media are provided in Table 1; the results indicate that ibrutinib is practically insoluble to slightly soluble in aqueous solutions. This solubility increases with decreasing pH, but the compound remains practically insoluble in the pH region between 3 and 8. Ibrutinib solubility in water as a function of pH is presented below in Figure 1.

Table 1: Ibrutinib Solubility in Aqueous Media as a Function of pH

Aqueous media	Temperature	Solubility (mg/mL)	USP Solubility
0.1N Hydrochloric Acid (HCl)	Ambient	1.6	Slightly soluble
0.1% Trifluoroacetic acid (pH=1.9)		0.25	Very Slightly Soluble
0.2% Formic Acid (FA) pH=3		0.06	Practically insoluble
Water (pH ~ 5.5)		0.003	Practically insoluble
10 mM Ammonium Acetate pH=4.5		0.003	Practically insoluble
10 mM Ammonium Acetate pH=6		0.003	Practically insoluble
10 mM Ammonium Acetate pH=8		0.003	Practically insoluble
0.3% SLS in water		1.05	Slightly Soluble
0.5% SLS in water		1.83	Slightly Soluble
0.065 N HCl	37.0 °C	1.42	Slightly Soluble
0.075 N HCl		1.69	Slightly Soluble
0.1 N HCl		2.50	Slightly Soluble
0.075 N HCl with 0.03% CTAB		1.82	Slightly Soluble
3.0% Tween 20 in Phosphate pH 6.8		0.63	Very Slightly Soluble
6.0% Tween 20 in Phosphate pH 6.8		1.28	Slightly Soluble

Figure 1: Ibrutinib solubility in water as a function of pH



As shown in Figure 1, Ibrutinib is poorly soluble in water, however, when protonated (pKa = 3.7-4.0), the solubility of ibrutinib in water is much higher. The solubility of ibrutinib is ~1.6 mg/mL at pH 1, 0.003 mg/mL in 10 mM ammonium acetate pH 4.5 and 0.003 mg/mL in 10 mM ammonium acetate at pH 8.

6. Polymorphism:

(b) (4)

7. Particle Size:

Ibrutinib is very slightly soluble in aqueous solutions, therefore particle size may affect dissolution rate and subsequently systemic absorption. The particle size specification of (b) (4) ibrutinib used throughout formulation and process development is the same as that used for the approved capsules (D[v, 0.9] = not more than (b) (4) µm). The commercial ibrutinib tablets will be manufactured with (b) (4) ibrutinib of the same particle size specification as the approved 140 mg capsules.

8. Formulation:

The drug product is an immediate release, film-coated tablet for oral administration, formulated with commonly used excipients. The tablets are available in four strengths, 140 mg, 280 mg, 420 mg and 560 mg, that are distinguished by size, color and shape.
The description of each tablet strength is provided in Table 2 and the composition is presented below in Table 3.

Table 2: Description of Ibrutinib Tablets

Strength	Description	Size (mm)
140 mg	Yellow-green to green round tablet. Debossed on one side with "ibr" and "140" on the other side.	(b) (4)
280 mg	Purple oblong tablet. Debossed on one side with "ibr" and "280" on the other side.	
420 mg	Yellow-green to green oblong tablet. Debossed on one side with "ibr" and "420" on the other side.	
560 mg	Yellow to orange oblong tablet. Debossed on one side with "ibr" and "560" on the other side.	

Table 3: Unit Composition of Ibrutinib Tablets 140 mg, 280 mg, 420 mg and 560 mg

Ingredient	Function	(b) (4) Strength (Label Claim)			
		140 mg Quantity/unit	280 mg Quantity/unit	420 mg Quantity/unit	560 mg Quantity/unit
Core Tablet					
Ibrutinib (b) (4)	Active	140.0	280.0	420.0	560.0
Lactose monohydrate	(b) (4)				(b) (4)
Croscarmellose sodium					
Sodium lauryl sulfate					
Povidone					
Microcrystalline cellulose					
Colloidal silicon dioxide					
Magnesium stearate[a] (b) (4)					
Total Core Tablets					
Film Coating (b) (4)					
Total Coated Tablets					(b) (4)

This Reviewer notes that the formulation contains Sodium lauryl sulfate (b) (4).

9. Dissolution method development:

(b) (4)

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(b) (4)

Reviewer's Comments: Based on the comparability of the formulation and the similar dissolution profiles of the clinical and registration batches it is concluded that the tablets used in the clinical studies are comparable to the registration and proposed commercial tablets and an in vitro bridge is established.

13. Overall review recommendations:

From a Biopharmaceutics perspective, NDA 210563 for Imbruvica® (Ibrutinib) Tablets, 140 mg, 280 mg, 420 mg, 560 mg is recommended for **APPROVAL**

Primary Biopharmaceutics Reviewer Name and Date:

Om Anand, Ph.D., 01/16/2018

Secondary Reviewer Name and Date:

Okpo Eradiri, Ph.D., 1/23/2018

Om Anand

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210563 Imbruvica® (Ibrutinib) Tablets, 140, 280, 420 and 560 mg

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 At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Dissolution – BCS Class II & IV	• Formulation • Raw Materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval, refer to BioPharm review.

Sherita McLamore

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