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

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