# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210563Orig1s000
# 210563Orig2s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

| Clinical Pharmacology Review | |
|---|---|
| **NDA** | NDA 210563 (SDN 001, eCTD 001) |
| **Type/Category** | Original submission |
| **Submission Date** | 09/12/2017 |
| **PDUFA** | 02/28/2018 |
| **Brand Name** | IMBRUVICA® |
| **Generic name** | Ibrutinib |
| **Formulation and Strength** | Tablets 140 mg, 280 mg, 420 mg and 560 mg |
| **Route of Administration** | Oral |
| **Applicant** | Pharmacyclics LLC |
| **Approved Indications** | Treatment of patients with:<br>• Mantle cell lymphoma (MCL) who have received at least one prior therapy;<br>• Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL);<br>• CLL/SLL with 17p deletion;<br>• Waldenström's macroglobulinemia (WM);<br>• Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.<br>• Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy |
| **Approved Dosing Regimen** | MCL and MZL: 560 mg taken orally once daily<br>CLL/SLL, WM and cGVHD: 420 mg taken orally once daily |
| **OCP Divisions** | Division of Clinical Pharmacology V (DCPV) |
| **OND Division** | Division of Hematology Products (DHP) |
| **OCP Primary Reviewer** | Liang Li, Ph.D. |
| **OCP Team Leader** | Olanrewaju Okusanya, Pharm.D.; M.S. |

# Contents



# List of Tables

## List of Figures

# 1. EXECUTIVE SUMMARY

Ibrutinib (IMBRUVICA®) is approved for the treatment of several B-cell malignancies and chronic graft versus host disease (cGVHD). In the current submission, the Applicant seeks the approval of a new tablet formulation at dose strengths of 140 mg, 280 mg, 420 mg, and 560 mg.

The Applicant submitted the study results of a relative bioavailability (BA) trial, a food effect trial, and two pivotal bioequivalence (BE) trials to support the to-be-marketed tablet formulation in 4 different strengths of 140 mg, 280 mg, 420 mg, and 560 mg for ibrutinib.

The review primarily focuses on:

1) the bioequivalence between ibrutinib to-be-marketed tablets and current available capsules;
2) food effect on to-be-marketed tablets.

The AUC of the to-be-marketed tablet was BE to that of the reference capsule at 140 mg and 560 mg dose strength. Although the $C_{max}$ of the to-be-marketed tablet was 10.2% lower at 140 mg and 27.7% lower at 560 mg as compared to the reference capsule formulation, such difference in $C_{max}$ is not expected to translate clinically meaningful impact on the effectiveness of ibrutinib. The food effect was generally comparable between tablet and capsule formulations. Overall, no clinically meaningful difference is expected between the reference capsule formulation and the to-be-marketed tablet formulation of ibrutinib.

## 1.1.Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted. The to-be-marketed tablet formulation at dose strengths of 140 mg, 280 mg, 420 mg, and 560 mg is considered approvable from a clinical pharmacology perspective. Dosing guidelines regarding food timings for ibrutinib tablets should follow the same recommendation for the ibrutinib capsules in the current labeling, i.e., there are no restrictions for food consumption when taking ibrutinib tablets or capsules.

## 1.2.Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

**Signatures:**

| | |
|---|---|
| **Liang Li, Ph.D.** | **Olanrewaju Okusanya, Pharm.D.; M.S.** |
| Clinical Pharmacology Reviewer | Acting Clinical Pharmacology Team Leader |
| Division of Clinical Pharmacology V | Division of Clinical Pharmacology V |

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.