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*APPLICATION NUMBER:*

**210563Orig1s000**

**210563Orig2s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

<b>Clinical Pharmacology Review</b>	
<b>NDA</b>	NDA 210563 (SDN 001, eCTD 001)
<b>Type/Category</b>	Original submission
<b>Submission Date</b>	09/12/2017
<b>PDUFA</b>	02/28/2018
<b>Brand Name</b>	IMBRUVICA®
<b>Generic name</b>	Ibrutinib
<b>Formulation and Strength</b>	Tablets 140 mg, 280 mg, 420 mg and 560 mg
<b>Route of Administration</b>	Oral
<b>Applicant</b>	Pharmacyclics LLC
<b>Approved Indications</b>	<p>Treatment of patients with:</p> <ul style="list-style-type: none"> <li>• Mantle cell lymphoma (MCL) who have received at least one prior therapy;</li> <li>• Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL);</li> <li>• CLL/SLL with 17p deletion;</li> <li>• Waldenström's macroglobulinemia (WM);</li> <li>• Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.</li> <li>• Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy</li> </ul>
<b>Approved Dosing Regimen</b>	<p>MCL and MZL: 560 mg taken orally once daily</p> <p>CLL/SLL, WM and cGVHD: 420 mg taken orally once daily</p>
<b>OCP Divisions</b>	Division of Clinical Pharmacology V (DCPV)
<b>OND Division</b>	Division of Hematology Products (DHP)
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## Contents

<b>1. EXECUTIVE SUMMARY .....</b>	<b>4</b>
1.1. RECOMMENDATIONS .....	4
1.2. POST-MARKETING REQUIREMENTS AND COMMITMENTS .....	4
<b>2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT .....</b>	<b>5</b>
2.1. PHARMACOLOGY AND CLINICAL PHARMACOKINETICS .....	5
2.2. DOSING AND THERAPEUTIC INDIVIDUALIZATION .....	5
2.2.1. <i>General dosing</i> .....	5
2.2.2. <i>Therapeutic individualization</i> .....	5
2.3. OUTSTANDING ISSUES .....	5
2.4. SUMMARY OF LABELING RECOMMENDATIONS .....	5
<b>3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW .....</b>	<b>6</b>
3.1. OVERVIEW OF THE PRODUCT AND REGULATORY BACKGROUND .....	6
3.2. GENERAL PHARMACOLOGICAL AND PHARMACOKINETIC CHARACTERISTICS .....	6
3.3. CLINICAL PHARMACOLOGY QUESTIONS .....	7
3.3.1. <i>Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?</i> .....	7
3.3.2. <i>Are there clinically relevant food-drug interactions for the to-be-marketed formulation and what is the appropriate management strategy?</i> .....	12
<b>4. APPENDICES .....</b>	<b>14</b>
4.1. SUMMARY OF BIOANALYTICAL METHOD VALIDATION AND PERFORMANCE .....	14
4.2. CLINICAL PK AND/OR PD ASSESSMENTS .....	14
4.2.1. <i>Trial 1021</i> .....	14
4.2.2. <i>Trial 1022</i> .....	15
4.2.3. <i>Trial 1019</i> .....	16

## List of Tables

Table 1: Summary of the Geometric Mean Ratios and 90% Confidence Intervals of the Ibrutinib PK Parameters from a Food Effect Trial and Two Pivotal Bioequivalence Trials .....	5
Table 2: Identity of Study Ibrutinib Formulations.....	7
Table 3: Summary of the Statistical Analysis of the Ibrutinib PK Parameters After Single Administration as Four 140-mg Oral Capsule of IMBRUVICA® or as one Single 560-mg Oral Tablet Under Fasted Conditions. ....	8
Table 4: Summary of the Statistical Analysis of the Ibrutinib PK Parameters After Single Administration as a 140-mg Oral Capsule of IMBRUVICA® or as a 140-mg Oral Tablet Under Fasted Conditions.....	8

Table 5: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg Oral Tablet of Under Fasted and Fed Conditions. ....13

Table 6: Summary of Bioanalytical Methods for Ibrutinib.....14

Table 7: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as Four 140-mg Capsules of IMBRUVICA® or as One Single 560-mg Oral Tablet Under Fasted Condition. ....15

Table 8: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as a 140-mg Capsules of IMBRUVICA® or as a 140-mg Oral Tablet Under Fasted Condition. ....16

Table 9: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg to-be-marketed Tablet Under Fasted and Fed Conditions. ....17

## List of Figures

Figure 1: BTK Occupancy of > 90% at Doses  $\geq 2.5$  mg/kg in Trial 04753. ....10

Figure 2: Predicted BTK Occupancy at Steady State after Administration of one 560-mg to-be-marketed Tablet and Four 140-mg Capsules Once Daily. ....10

Figure 3: Dose-response Relationship for ORR in Phase 1 Dose Escalation Trial PCYC-04753. ....11

Figure 4: Bar Chart ( $\pm 99\%$  CIs) of Overall Response Rate in Patients with CLL (Trials 1102, 1112, 1115, 1117, CLL3001, 04753 in NDA205552) Classified by Ibrutinib  $C_{max,ss}$  Quartile.....11

Figure 5: Bar Chart ( $\pm 99\%$  CIs) of Overall Response Rate in Patients with CLL (Trials 1104, MCL2001, MCL3001, 04753 in NDA205552) Classified by Ibrutinib  $C_{max,ss}$  Quartile. ....12

Figure 6: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as Four 140-mg Capsules of IMBRUVICA® or as one Single 560-mg to-be-marketed Tablet Under Fasted Conditions.....15

Figure 7: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as a 140-mg Capsules of IMBRUVICA® or as a 140-mg to-be-marketed Tablet Under Fasted Conditions. ....16

Figure 8: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg to-be-marketed Tablet Under Fasted and Fed Conditions.....17

## 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:**

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**Liang Li, Ph.D.**

Clinical Pharmacology Reviewer

Division of Clinical Pharmacology V

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