CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210563Orig1s000
210563Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 7, 2018
From	Tanya Wroblewski, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	210563
Applicant	Pharmacyclics, LLC
Date of Submission	August 31, 2017
PDUFA Goal Date	February 28, 2018
Proprietary Name	Imbruvica®
Established or Proper Name	Ibrutinib
Dosage Form(s)	Tablets 140mg, 280mg, 420mg and 560mg, for oral use
Applicant Proposed Indication(s)/Population(s)	No new indications, provides new dosage formulation -Mantle cell lymphoma (MCL) (accelerated approval) -Marginal zone lymphoma (MZL)who require systemic therapy and have received at lea anti-CD20 based therapy (accelerated approval) -Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) -CLL/SLL with 17p deletion -Waldenström's macroglobulinemia (WM) -Chronic Graft vs. Host disease (cGVHD) after failure of one or more lines of systemic therapy
Applicant Proposed Dosing Regimen(s)	No new dosing regimen, provides new dosage formulation.
Recommendation on Regulatory Action	*Accelerated Approval: This NDA provides new tablet formulation, existing NDA 205552 for ibrutinib still has accelerated approval for some of the indications, thus these PMRs will carry over and as such approval of new tablets will be accelerated approval.*
Recommended Indication(s)/Population(s) (if applicable)	*Not applicable*
Recommended Dosing Regimen(s) (if applicable)	*New dosage form: 140mg, 280mg, 420mg, and 560mg tablets for oral use. Dosing regimen remains the same.*

1. Benefit-Risk Assessment

This application provides CMC and clinical pharmacology data to support stability and bioequivalence of a new tablet formulations for Ibrutinib; this application is not a new molecular entity. There was no new clinical efficacy or safety data included in this NDA and therefore no need for benefit-risk assessment. There are no updates to the indication, efficacy or safety sections of the USPI.

The Applicant seeks approval of a new tablet formulation at dose strengths of 140mg, 128mg, 420mg and 560mg. The tablets will have the same indications and dosing as the currently marketed ibrutinib capsules. The new tablet formulations are intended to improve pill burden and provide for appropriate doses with a single tablet.

Recommend approval of the new tablet formulation at dose strengths of 140mg, 280mg, 420mg and 560mg for the approved indications for Ibrutinib. This application will receive accelerated approval as two of the existing indications for ibrutinib are accelerated approvals and the PMRS will carry over to this application.

2. Background

Imbruvica® (Ibrutinib, also known as PCI-32765) is a first-in-class, orally administered inhibitor of Bruton Tyrosine Kinase (BTK) that was co-developed by Pharmacyclics, LLC and Janssen Research & Development, LLC for the treatment of B-cell malignancies.

Ibrutinib is currently approved for the treatment of patients with mantle cell lymphoma (MCL) who have received one prior therapy, chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), CLL/SLL with 17p deletion, marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20 based therapy, Waldenström's macroglobulinemia (WM), and chronic graft versus host disease (cGVHD).

Ibrutinib is currently available as 70mg and 140mg capsules. The recommended doses are (b) (4) mg once daily for MCL and MZL and 420mg once daily for CLL/SLL, WM and cGVHD. The recommended dose for patients with mild hepatic impairment is 140mg and for patients with moderate hepatic impairment is 70mg.

Patients receiving ibrutinib at the current recommended doses (either 480 or 520mg) are currently required to take multiple 140mg capsules daily. This may result in missed doses or incomplete doses and places and additional burden on patients. The new tablet formulations will provide for appropriate doses with a single tablet and will reduce pill burden and potentially missed doses or incomplete doses.

This submission primarily pertains to clinical pharmacology and chemistry manufacturing and controls.

No new clinical efficacy data were submitted with this supplement. The tablet formulations are relevant to all the current indications for patients who currently take multiple capsules of Imbruvica®. Refer to complete clinical pharmacology review for analysis of drug-drug interaction data and bioequivalence data provided with this supplement.

Please refer to the reviews by each specific discipline under NDA 205552 for details pertaining to original NDA submission as well as details relevant to each specific indication.

3. Product Quality

There are no outstanding product quality issues with this application. All site inspections were complete and there are no outstanding issues. Please refer to the CMC review by Sherita D. McLamore, Ph.D. for additional details.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues with this application.

5. Clinical Pharmacology

The Applicant submitted study results of a bioavailability trial, food effect trial and two pivotal bioequivalence trials to support the proposed new tablet formulation in 4 different strengths of 140mg, 280mg, 520mg, 560mg for ibrutinib. The clinical pharmacology review focused on the bioequivalence between ibrutinib to be marketed tablets and current available capsules and food effect on the new tablets. .

Bioequivalence evaluations demonstrated no clinically significant difference in AUC between the tablet and capsule formulations at the 140 and 520mg doses. There was a Cmax decreases of 10.2% and 27.7% at the 140mg and 520mg doses respectively.

From the review by Liang Li, Ph.D.

“The AUC of the to-be-marketed tablet was BE to that of the reference capsule at 140mg and 560mg dose strength. Although the Cmax of the to-be-marketed tablet was 10.2% lower at 140mg and 27.7% lower at 560mg as compared to the reference capsule formulation, such difference in Cmax is not expected to translate clinically meaningful impact on the effectiveness of ibrutinib. The fold 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.”

The Office of Clinical Pharmacology reviewed the information submitted by the Applicant. The Office of Clinical Pharmacology tablets formulation at dose strengths of 140mg, 280mg, 420mg and 560mg is considered approvable from a clinical pharmacology perspective. Per the clinical

pharmacology review, “the dosing guidelines regarding food timings for ibrutinib tablets should follow the same recommendation for ibrutinib capsules in current labeling, i.e., there are no restrictions for food consumption when taking ibrutinib tablets or capsules.”

6. Clinical Microbiology

There are no clinical microbiology issues with this application.

7. Clinical/Statistical- Efficacy

There was no new efficacy data submitted with this application.

8. Safety

There was no new safety data submitted with this application.

The most common adverse reactions in patients with cGVHD are fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia and pneumonia.

The U.S. Prescribing Information (USPI) for Imbruvica® includes Warnings and Precautions for hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome, and embryo-fetal toxicity.

9. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant safety or efficacy issues.

10. Pediatrics

FDA granted Orphan Drug Designation for ibrutinib in 2013 for the treatment of patients with relapsed or refractory mantle cell lymphoma. There is one ongoing trial evaluating the safety and efficacy of ibrutinib in pediatric and young adult patients with relapsed or refractory mature B-cell Non-Hodgkin Lymphoma. Currently there is limited information on the use of ibrutinib in pediatric patients.

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