CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig2s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 205552 (Original-2 for CLL indication)
Applicant	Pharmacyclics, Inc.
Date of Submission	28 June 2013
PDUFA Goal Date	28 February 2014
Proprietary Name / Established (USAN) names	Imbruvica/ibrutinib
Dosage forms / Strength	Capsules, 140 mg
Proposed Indication(s)	Treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
Recommended:	*Accelerated Approval*

Material Reviewed/Consulted	Reviewers
Division Director Review	Ann Farrell, MD
Regulatory Project Manager Review	Diane Hanner
Clinical Review	Nicole Verdun, MD/ R. Angelo de Claro, MD
Statistical Review	Yun Wang, PhD/ Lei Nie, PhD
Pharmacology Toxicology Review	Shwu-Luan Lee, PhD, Haw-Jyh (Brian) Chiu, PhD, George Ching-Jey Chang, PhD, Margaret E. Brower, PhD/ Haleh Saber, PhD/ John Leighton, PhD
ONDQA-CMC and Biopharmaceutic Reviews	CMC: Donghao (Robert) Lu, PhD (Drug substance)/ Xiao-Hong Chen, PhD (Drug product)/ Biopharm: John Duan, PhD /Angelica Dorantes, PhD Microbiology: Bryan Riley, PhD ONDQA: Ramesh Sood, PhD (Tertiary Review)
Clinical Pharmacology Review	Elimika Pfuma, PharmD, PhD, Julie Bullock, PharmD, Rosane Charlab Orbach, PhD, Bahru Habtemariam, PharmD, Yuzhuo Pan, PhD, Anshu Marathe, PhD, Ping Zhao PhD
OSI/DGCPC	Anthony Orencia, MD/ Janice Pohlman, MD, MPH
OSE/DRISK	Joyce Weaver, PharmD/ Cynthia LaCivita, PharmD
OSE/DMEPA	Kevin Wright, PharmD/ Yelena Maslov, PharmD
OSE/DPV	Katherine Coyle, PharmD/ Tracy Salaam, PharmD
Patient Labeling Team (DMPP)	Karen Dowdy, RN, BSN / Barbara Fuller RN, MSN

1. Introduction

On June 28, 2013, Pharmacyclics Inc. submitted NDA 205552 for two indications: (1) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy and (2) for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. The application was administratively split into NDA 205552/Original-1 for the MCL indication and NDA 205552/Original-2 for the CLL indication. NDA 205552/Original-1 received accelerated approval for the treatment of patients with MCL who have received at least one prior therapy on November 13, 2013. The subject of this review is NDA 205552/Original-2 for the CLL indication.

Imbruvica (ibrutinib) is a first-in-class Bruton's tyrosine kinase inhibitor, which targets the B-cell antigen receptor (BCR) signaling pathway.

The primary basis for the application is the result from clinical trial PCYC-1102-CA, an open-label, single-arm trial of Imbruvica monotherapy in 48 patients with CLL who have received at least one prior therapy.

2. Background

CLL is the most common form of leukemia in adulthood. The National Cancer Institute estimates that 15,680 men and women (9,720 men and 5,960 women) will be diagnosed with CLL in 2013. CLL is a lymphoproliferative neoplasm characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymphatic organs.

Current treatments for CLL are not curative, and relapse, toxicity, and resistance to therapy provide for an unmet medical need. Among patients who relapse or who are refractory to first line treatment, the choice of subsequent therapy depends on age, duration of response to prior therapy, ability to tolerate treatment, disease related manifestations, and the presence of molecular poor-risk features.

The following treatments are FDA-approved for the treatment of CLL: Chlorambucil (1957), Cyclophosphamide (1959), Fludarabine (1991), Alemtuzumab (2007), Bendamustine (2008), Ofatumumab (2009, accelerated approval), Rituximab (2010), and Obinutuzumab (2013).

3. CMC/Device

CMC sections were addressed in the NDA 205552 (Original-1) review. There are no major labeling changes proposed for the CMC sections with NDA 205552 (Original-2).

4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology and Toxicology sections were addressed in the NDA 205552 (Original-1) review. There are no major labeling changes proposed for the Nonclinical Pharmacology and Toxicology sections with NDA 205552 (Original-2).

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology reviewed the MCL and CLL indications together in the NDA 205552 (Original-1) review, and issued a brief addendum for NDA 205552 Original-2. There are no major labeling changes proposed for the Clinical Pharmacology sections with NDA 205552 (Original-2).

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 3 of NDA 205552 (Original-1) review for product quality microbiology information.

7. Clinical - Efficacy

The approval in CLL is based on the results of a multi-center, single-arm trial of 48 patients with previously treated CLL. The median age was 67 years (range, 37 to 82 years) and 71% were male. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6.7 years and the median number of prior treatments was 4 (range, 1 to 12 treatments). Ibrutinib was administered orally at 420 mg once daily until disease progression or unacceptable toxicity.

The efficacy results demonstrated a 58.3% overall response rate (95% CI: 43.2, 72.4) as assessed by an independent review committee. No complete responses were observed. The response duration ranged from 5.6 to 24.2+ months; the median was not reached.

As a condition of this accelerated approval, the sponsor is required to submit results of randomized clinical trial(s.) In January 2014, Pharmacyclics notified FDA of the early stopping of the RESONATE trial by the Data Monitoring Committee (DMC) based on favorable results of a planned interim analysis. RESONATE, a phase 3 clinical trial, randomized patients to either ibrutinib or ofatumumab. Patients entered on this trial had previously treated CLL or small lymphocytic lymphoma (SLL) and were not considered candidates for treatment with purine analogue-based treatments. The trial was reported to demonstrate an improvement in progression-free survival and overall survival.

8. Clinical - Safety

The safety profile of ibrutinib for patients with previously treated CLL was consistent with observations in the mantle cell lymphoma clinical trial. The most common adverse reactions reported in the CLL clinical trial (occurring in greater than or equal to 20% of patients) were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness.

9. Advisory Committee Meeting

The NDA for this new molecular entity was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

Imbruvica is exempt from the pediatric study requirements in 21 CFR 314.55. The FDA Office of Orphan Products Development granted Orphan Drug Designation for ibrutinib for the treatment of CLL on April 6, 2012. Imbruvica has not been evaluated in pediatric patients.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Accelerated Approval

- Risk Benefit Assessment

Relapsed CLL is a serious and life-threatening illness. The efficacy and safety results in clinical trial PCYC-1102-CA demonstrate an acceptable benefit-risk profile for Imbruvica for the treatment of patients with previously treated CLL.

The response rate of 58.3% (95%CI: 43.2%, 72.4%) in a patient population with relapsed CLL, with a duration of response ranging from 5.6 to 24.2+ months support approval. However, verification of clinical benefit of Imbruvica in the CLL population is necessary due to the small number of patients treated, none of the patient achieved a complete response, and time-to-event endpoints such as PFS or overall survival cannot be adequately interpreted in single-arm trials. Therefore, the sponsor will be required to verify clinical benefit under accelerated approval regulations. During the review, the Applicant notified the Agency regarding early stopping of the RESONATE trial (PCYC-1112-CA), a Phase 3, randomized controlled trial of ibrutinib or ofatumumab in patients with previously treated CLL due to significant improvements in PFS and overall survival in the ibrutinib arm. Although the results have not been submitted to the Agency, a subsequent submission is planned for this trial and may serve as the demonstration of clinical benefit.

The risk-benefit profile of Imbruvica was discussed in the reviews of Drs. Farrell, De Claro, and Verdun and I concur with their recommendation to grant accelerated approval for this NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  A REMS to assure safe use of ibrutinib is not recommended.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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