CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See stamp date
From	R. Angelo de Claro, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205552 (Original-2)
Applicant	Pharmacyclics, Inc.
Date of Submission	28 June 2013
PDUFA Goal Date	28 February 2014
Proprietary Name / Established (USAN) names	Imbruvica
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:	Approval

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

1. Introduction

On June 28, 2013, Pharmacyclics Inc. (Applicant) submitted NDA 205552 Original-2 proposed for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. The Applicant had submitted a concurrent application (NDA 205552 Original-1) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy also on June 28, 2013, and received accelerated approval for the treatment of patients with MCL who have received at least one prior therapy on November 13, 2013.

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

Chronic lymphocytic leukemia (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/Statistical- Efficacy

I agree with the conclusions of the statistical and clinical reviewers for the efficacy of Imbruvica for patients with CLL who have received at least one prior therapy.

The following summarizes the key milestones in the regulatory history. The Applicant submitted the IND for ibrutinib (PCI-32765) on September 8, 2008. Protocol PCYC-1102-CA (single-arm trial in patients with CLL/SLL) was initiated on March 11, 2010. End of Phase 2 (EOP2) meetings to discuss the CLL clinical development program including registrational approach occurred on December 5, 2011, April 30, 2012, July 26, 2012, and September 26, 2012. Fast Track was granted on October 29, 2012 for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have relapsed or have refractory disease and have previously received at least one prior therapy. On March 18, 2013, Breakthrough Therapy designation was granted by the FDA for the treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma with deletion of the short arm of chromosome 17 (del 17p). Pre-NDA meeting occurred on April 9, 2013.

Efficacy Summary

The safety and efficacy of Imbruvica in patients with CLL who have received at least one prior therapy were evaluated in an open-label, multi-center trial of 48 previously treated patients. The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The

median time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor ≥ 5 cm.

Imbruvica was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. Overall response (ORR) and duration of response (DOR) were assessed using a modified version of the International Working Group CLL Criteria by an Independent Review Committee. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

Primary Reviewer Conclusions
The statistical reviewer concluded that Imbruvica provided durable treatment effect for patients with relapsed or refractory chronic lymphocytic leukemia in Study PCYC-1102-CA.

CDTL Comment: The statistical review was finalized prior to agreement with the Applicant on the ORR results. The ORR of 58.3% (28/48) is acceptable to both the clinical and statistical teams, and differs from the final ORR (56.3%, 27/48) reported in the statistical review based on clarification provided by the Applicant regarding the response profile of 1 patient.

The clinical reviewer concluded that the Applicant has demonstrated the efficacy of Imbruvica in patients with chronic lymphocytic leukemia who have been previously treated.

CDTL Comment: At the time of application submission, the clinical and statistical teams noted lack of independent review committee (IRC) verification of the efficacy results. During the review cycle, the Applicant submitted the requested IRC assessments for the efficacy endpoints.

8. Safety

I concur with the clinical reviewer's conclusions regarding the safety of Imbruvica for the proposed CLL indication.

Safety Summary
The safety profile of Imbruvica was primarily evaluated in 48 patients with previously treated CLL enrolled in PCYC-1102-CA, a single-arm Phase 2 clinical trial. A summary of the key safety findings based on the data cut-off date of December 26, 2013 is listed below:

- The Imbruvica dose was 420 mg once daily. The median exposure duration was 15.6 months.

- All treated subjects experienced at least 1 treatment-emergent adverse event.

- Fifty-eight percent of patients had at least one bleeding event, characterized as bruising (54%), epistaxis (6%), eye related hemorrhage (6%), rectal hemorrhage (4%), or subdural hematoma (4%). Seventeen percent of patients experienced petechiae during the clinical trial.

- The most common non-hematological adverse events (occurring in ≥ 20% of patients) were diarrhea (63%), upper respiratory tract infection (39%), fatigue (33%), pyrexia (25%), peripheral edema (23%), arthralgia (23%), constipation (22%), stomatitis (21%), sinusitis (21%), nausea (21%), and dizziness (21%).

- The most common Grade 3 or 4 adverse events (occurring in ≥ 5% of patients) were neutropenia, pneumonia, thrombocytopenia, hypertension, dehydration, and sinusitis.

- Forty-two percent of patients required a dose modification or interruption due to an adverse event. The most common adverse events leading to a modification or interruption were infections (19%).

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. 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. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.
- **Financial Disclosures:** A concern with respect to possible bias arose from the large monetary donations to the two sites with the largest enrollment into Trial [redacted] (b) (6) which enrolled 22 (46% of total) patients and [redacted] (b) (6) which enrolled 15 (31% of total) patients. Both sites were inspected by the Office of Scientific Integrity (OSI), and the inspectors verified that the conduct of the trial complied with U.S. laws and regulations covering good clinical practices. In addition, the implementation of an IRC review for verification of efficacy mitigates this concern.
- **Other GCP Issues:** None

- **Office of Scientific Investigation (OSI) Audits:** The following is from the executive summary of the findings:

  For Protocol PCYC-1102-CA, two U.S. clinical investigation sites were inspected in support of the application (MD Anderson and Ohio State University). The clinical site inspections reviewed the records of 45 subjects were screened and 42 subjects were enrolled. Thirty-two subjects were rolled over into a long-term extension study, under Protocol 1103. A complete audit of 16 subjects' records including verification of the informed consent documents of 16 enrolled subjects was performed.

  Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Specific records were reviewed for study participants' inclusion or exclusion criteria, drug accountability, adverse events, monitoring, IRB approval, financial disclosure forms, and overall protocol compliance. There was no evidence of under-reporting of significant adverse events.

  No significant regulatory violations were noted during the FDA inspection and a Form FDA 483 was not issued.

  The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

- **Other discipline consults**: None
- **Other outstanding regulatory issues**: None

12. Labeling

- **Proprietary name.** On 16 August 2013, OSE/DMEPA concluded that the proposed proprietary name, Imbruvica is acceptable.

- **OSE/DPV.** There were no new OSE/DPV concerns with NDA 205552 Original-2. Action letter will include reminder for PMR 2060-4, pharmacovigilance plan for serious hemorrhagic events. Refer to OSE/DPV review for NDA 205552 Original-1.

- **OSE/DRISK.** There were no new OSE/DRISK concerns with NDA 205552 Original-2. Refer to OSE/DRISK review for NDA 205552 Original-1. Based on the currently available information, REMS is not recommended.

- **OSE/DMEPA.** There were no new OSE/DMEPA concerns with NDA 205552 Original-2. Refer to OSE/DMEPA review for NDA 205552 Original-1.

- **Patient Labeling Team.** The patient labeling group participated in the labeling discussions.

- **OPDP.** OPDP attended labeling meetings and provided input. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: 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. All review team members recommend approval.

  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, multiple uncertainties remain regarding the clinical benefit of Imbruvica in the CLL population.

  Section 21 CFR 314.510 addresses approval based on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

  - The small number of patients (N=48) treated at the proposed dosing regimen (420 mg per day) raises uncertainty on the magnitude of effect on response rate as evidenced by the confidence interval spanning 43% to 72%.

  - None of the patients achieved a complete response.

  - Time-to-event endpoints such as progression-free survival or overall survival cannot be adequately interpreted in single-arm trials due to confounding effects of the disease course.

  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 progression-free survival and overall survival in the ibrutinib arm. Although the results have not been verified by the Agency, this news is encouraging regarding fulfillment of accelerated approval requirements.

  CDTL Recommendation: Accelerated approval

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  The Applicant did not propose a REMS and the review teams did not identify the need for a REMS at this time to ensure the safe use of Imbruvica.

- Recommendation for other Postmarketing Requirements and Commitments

  For fulfillment of accelerated approval (Subpart H) requirements, the Applicant has agreed to the following postmarketing requirements:

  PMR-1: Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

  PMR-2: Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.

  Successful completion of either PMR-1 or PMR-2 could verify clinical benefit and fulfill accelerated approval requirements for the Chronic Lymphocytic Leukemia (CLL) indication.

  Refer to action letter for final wording of the post-marketing requirements and commitments.

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/s/

ROMEO A DE CLARO
02/11/2014