

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205552Orig2s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	205552-02
Supplement #	
Applicant Name	Pharmacyclics and Janssen Research and Development
Date of Submission	June 28, 2013
PDUFA Goal Date	February 28, 2014
Proprietary Name / Established (USAN) Name	Imbruvica/ibrutinib/PCI-32765
Dosage Forms / Strength	140 mg hard gelatin capsules
Proposed Indication(s)	Indicated for the treatment of patients with chronic lymphocytic lymphoma who have received prior therapy
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Nicole Verdun, M.D./ Angelo DeClaro, 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.
CMC Review/OBP Review	Donghao Lu, Ph.D./Xiao Chen, Ph.D./Janice Brown, M.S./Ali Al-Hakim, Ph.D./Ramesh K. Sood, Ph.D./John Z. Duan, Ph.D./Angelica Dorantes, Ph.D.
Microbiology Review	Brian S. Riley, Ph.D./ Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Elimika Pfuma, Pharm.D., Ph.D./Julie Bullock, Pharm.D./Rosane Charlab Orbach, Ph.D./Bahru Habtemariam, Ph.D./Yuzhuo Pao, Ph.D./Anshu Marathe, Ph.D./Ping Zhao, Ph.D.
DDMAC	Nisha Patel/Karen Rulli
OSI	Anthony Orenica, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review	Angelo DeClaro, M.D.
OSE/DMEPA	Kevin Wright, Pharm.D./Yelena Maslov, Pharm. D./ Carol Holquist, R. Ph.
OSE/DPV	Katherine Coyle, Pharm.D. / Tracy Salaam, Pharm.D.
OSE/DRISK	Joyce Weaver, Pharm.D. / Cynthia LaCivita, Pharm.D.

Other -OMP	Karen Dowdy, RN, BSN/Nisha Patel, Pharm.D./ LaShawn Griffiths,MSHS-PH, BSN,RN/ Barbara Fuller, RN, MSN, CWOCN
Other-IRT	Kevin M. Krudys, Pharm.D./Qianyu Dang/Monica L. Fizzman/Norman Stockbridge,M.D.

Signatory Authority Review Template

1. Introduction

On June 28, 2013, Pharmacyclics, Inc. filed a new drug application (NDA) for ibrutinib. Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk).

The FDA therapeutic class designation is a kinase inhibitor.

The original application had two indications and was administratively split into the mantle cell indication (original 01) and the chronic lymphocytic lymphoma indication (original 02). This summary review concerns the chronic lymphocytic lymphoma indication.

The clinical support for the proposed indication is from clinical trial PCYC-1102-CA, an ongoing, an open-label, single-arm trial of ibrutinib monotherapy in 48 patients with CLL who have received at least one prior therapy.

The applicant proposes an oral dosing regimen of 420 mg once daily for patients with CLL. This proposed dosing is lower than the dose approved for the treatment of mantle cell lymphoma.

The application was filed as a priority review. The PDUFA goal date for the current submission is February 28, 2014.

Imbruvica/ibrutinib is marketed in the United States but not for the treatment of CLL.

2. Background

The following text is from Dr. DeClaro's review. I concur with his statements.

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 Obinituzumab (2013).

3. CMC/Device

From the primary review for the original 01 submission:

From a CMC perspective, this application is recommended for Approval. EES has an overall "Acceptable" recommendation for this NDA. ...

Based on the available stability data an 24-month expiry dating is granted for Imbruvica® ibrutinib capsules stored at temperature of 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

The biopharmaceutics review recommends a post-marketing commitment to collect additional dissolution profile data (release and stability).

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified.

From the primary review for the original 01 submission:

Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk); it binds covalently to a cysteine in the active site of Btk....

The general toxicology studies in rats and dogs identified GI tract, lymphoid tissues, bone and skin as the main target of toxicities...

Ibrutinib was not mutagenic in bacterial Ames test or clastogenic in a chromosome aberration test in Chinese Hamster Ovary cells (CHO). Ibrutinib did not increase

micronucleus formation in mice after oral doses up to 2000 mg/kg. The mutagenicity of impurities was assessed through Ames test or by 2 computational SAR analyses (DEREK Nexus and MultiCase). The impurities tested were not mutagenic.

Reproductive and developmental toxicities of ibrutinib were investigated in rats and rabbits....

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Increased post-implantation loss and increased resorption occurred at the high dose of 80 mg/kg. Fetal toxicities (visceral malformations and variations, and skeletal variations) were observed at the high dose of 80 mg/kg. Reduced fetal weight was seen at ibrutinib doses at 40 mg/kg and 80 mg/kg. The dose of 80 mg/kg resulted in maternal toxicities. The dose of 80 mg/kg/day in animals resulted in exposures (total AUC) approximately 14 times the AUC in patients with MCL (ibrutinib dose of 560 mg/day) and 20 times the AUC in patients with CLL (ibrutinib dose of 420 mg/day). The exposure at 40 mg/kg/day was approximately 6 times the AUC in patients with MCL and 8 times the AUC in patients with CLL.

In a non-GLP study conducted in rabbits, ibrutinib was administered orally to pregnant animals during the period of organogenesis at doses of 10, 30, and 100 mg/kg/day. At the ibrutinib dose of 100 mg/kg, which is greater than the maternally-toxic dose (≥ 30 mg/kg/day), there were embryo-fetal toxicities. Findings included increases in resorption and implantation loss, decreases in viable fetuses and fetal body weights, as well as spontaneous abortions.

Ibrutinib did not cause adverse findings in male or female reproductive organs in general toxicology studies.

5. Clinical Pharmacology/Biopharmaceutics

From the Clin Pharm review for the original 01 submission:

Ibrutinib is primarily metabolized by CYP3A4. No dose reduction is recommended for weak CYP3A4 inhibitors, but a dose reduction to 140 mg is recommended for concomitant use of a moderate CYP3A4 inhibitor. A dose recommendation could not be made for strong CYP3A4 inhibitors due to the 24-fold increase in exposure. Therefore, it is recommended that concomitant use be avoided for chronic CYP3A4 inhibitors and the dose of ibrutinib can be temporarily interrupted during the use of a short-term CYP3A4 inhibitor (≤ 7 days). A 7 day interruption of ibrutinib dosing was supported by data from the pivotal trial where patients responded to therapy even when they required short term dose interruption during therapy. The concomitant use of strong CYP3A4 inducers should be avoided. There is insufficient data to recommend a dose of ibrutinib in patients with hepatic impairment. A PMR will be issued for the submission of the study report for the ongoing hepatic impairment trial.

The following are the proposed PMRs from the Clin Pharm review team's review:

1. *Submit the final study report for trial PCI-32765CLL1006 entitled, “An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects with Varying Degrees of Hepatic Impairment”.*
2. *Submit the final study report for trial PCI-32765CLL1010 entitled, “An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects”.*

(b) (4)

The food effect study demonstrated a two-fold increase in exposure when ibrutinib was administered with a high-fat meal compared to overnight fast.

No issues that would preclude approval were identified.

6. Microbiology

No issues that would preclude approval were identified in the review of original 01.

7. Clinical/Statistical-Efficacy

The clinical team reviewed the application. The following text is from the CDTL review:

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 \geq 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.

I agree with the conclusions of the clinical and statistical review team recommending approval for this application under the accelerated approval regulations. I recommend that the labeling provide a range for the duration of response.

I concur with the recommendations of the primary reviewer and CDTL regarding the recommendation for accelerated approval.

8. Safety

No new safety issues were identified during the review of this portion of the application. The following text is from the CDTL review:

Safety Summary

- *The ibrutinib 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 $\geq 20\%$ 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 $\geq 5\%$ 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%).*

This summary highlights what has been observed in a limited number of patients. Based on the potential for serious adverse reactions – bleeding/bruising risk, myelosuppression, and infection are identified as the most serious. Peripheral lymphocytosis has been observed with this agent.

I have read the primary review and secondary review and concur with their recommendation.

9. Advisory Committee Meeting

This application is the second indication under the original NDA submission. The application for the treatment of mantle cell was approved in 2013. This is the fourth application within the past several years for an indication to treat chronic lymphocytic leukemia. This application was not taken to an Oncologic Drugs Advisory Committee meeting because there were no issues with the trial design, conduct, endpoint or data analysis. In addition the trial results demonstrated a positive risk benefit and no safety issues arose during the review of the application requiring an expert committee meeting.

10. Pediatrics

This product has orphan designation therefore is exempt from the requirement to conduct studies in pediatric patients.

11. Other Relevant Regulatory Issues

Financial Disclosure information was provided and reviewed. The information provided did not suggest any integrity issue. In addition an independent review committee reviewed the clinical response data.

From the Office of Scientific Investigation review:

The study data collected appear generally reliable in support of the requested indication.

12. Labeling

All disciplines made recommendations for labeling. The recommendations were discussed during internal labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
Approval under 21 CFR 314.500 -- Accelerated Approval with requirements for trials to confirm clinical benefit.

The clinical trial database for the accelerated approval is admittedly small. However 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. The Applicant decided to stop the trial early due to significant improvements in progression-free survival and overall survival in the ibrutinib arm. The Applicant shared the top-line results with the Agency and although the top-line results have not been verified by the Agency, this news suggests the Applicant will be able to submit a supplement relatively soon allowing fulfillment of accelerated approval requirements.

- Risk Benefit Assessment

CLL remains an incurable disease at this time. Ibrutinib has demonstrated a durable response rate in a small single arm trial. Safety issues include bleeding/bruising risk, myelosuppression, infection, gastrointestinal disturbance, rash, musculoskeletal pain, and peripheral edema. Based on the submitted data the risk-benefit profile appears favorable.

- Recommendation for Post marketing Risk Management Activities

See original 01 approval letter for information regarding enhanced pharmacovigilance.

Please see approval letter for exact wording.

- Recommendation for other Post marketing Study Requirements/ Commitments

The PMRs/PMCs will address the following issues:

Accelerated approval – 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.

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

In addition, the Applicant has several PMRs/PMCs that are described in the original 01 approval letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
02/11/2014