# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205552Orig2s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Ann. T. Farrell, M.D., Division Director |
| **Subject** | Division Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | 205552-02 |
| **Applicant Name** | Pharmacyclics and Janssen Research and Development |
| **Date of Submission** | June 28, 2013 |
| **PDUFA Goal Date** | February 28, 2014 |
| **Proprietary Name /**<br>**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**<br>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. |

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|---|---|
| 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. Fiszman/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:*

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