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APPLICATION NUMBER:

205552Orig1s000

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 # **Supplement #**	205552
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 mantle cell lymphoma
Action/Recommended Action for NME:	**Accelerated Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Karen McGinn, M.S.N. C.R.N.P./ Angelo DeClaro, M.D.
Statistical Review	Yun Wang, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Shwu Luan Lee, 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. 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 applicant submitted a request to be designated as a Breakthrough Therapy and the designation was granted. The applicant has proposed the following indication: "for the treatment of patients with mantle cell lymphoma".

(b) (4) This summary review concerns the mantle cell indication.

The clinical support for the proposed indication is from clinical trial PCYC-1104-CA, an ongoing, open-label, single-arm trial of ibrutinib monotherapy in 111 patients with MCL who have received at least one prior therapy.

The applicant proposes an oral dosing regimen of 560 mg once daily for patients with MCL.

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

Imburivca/ibrutinib is not marketed in any country.

2. Background

Mantle cell lymphoma (MCL) is a relatively rare form of Non-Hodgkin Lymphoma (NHL) and represents approximately 5-9 % of all new NHL cases per year. Several

subtypes of MCL exist: centrocytic, small cell type and blastoid variant. The chromosomal translocation t(11;14) is the hallmark of MCL and this translocation results in the overexpression of cyclin D1. MCL has a male predominance, with an incidence rate 2.5 times higher than that of females. The median age at diagnosis is 68 years. Patients typically present with generalized lymphadenopathy, and extranodal involvement is common particularly the gastrointestinal tract, blood, bone marrow and spleen.

There is no curative therapy for MCL except for those patients who undergo an allogeneic stem cell transplantation. However the median age at diagnosis means that an allogeneic stem cell transplant is not an option for many patients. The median overall survival in patients with newly-diagnosed MCL is 3 to 5 years. First-line treatment regimens include multi-agent chemotherapy regimens, however, almost all patients will eventually relapse.

FDA approved agents for the treatment of MCL include Velcade and Revlimid. Both were approved for patients with MCL who had received at least 1 prior therapy. The Velcade approval was based on demonstration of an overall response rate (ORR) of 31%, complete response (CR) rate of 8%, and a median duration of response (DOR) of 9.3 months. The Revlimid approval was based on demonstration of an ORR 26%, CR 7%, and median DOR of 16.6 months.

3. CMC/Device

From the primary review:

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:

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) [redacted] (b) (4) *The exposure at 40 mg/kg/day was approximately 6 times the AUC in patients with MCL* [redacted] (b) (4)

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:

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

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