

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205552Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

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

<b>Material Reviewed/Consulted</b>	
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) (b) (4)*

*The exposure at 40 mg/kg/day was approximately 6 times the AUC in patients with MCL (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 ( $\geq 30$  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 ( $\leq 7$  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**

N/A

## **7. Clinical/Statistical-Efficacy**

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

### **Efficacy Summary**

*The efficacy of ibrutinib was primarily evaluated in 111 patients with previously treated MCL enrolled in PCYC-1104-CA, a single-arm Phase 2 clinical trial. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor  $\geq 5$  cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.*

*Ibrutinib was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this clinical trial was investigator-assessed overall response rate (ORR). Responses to ibrutinib are shown in Table 2.*

**Table 2: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma**

	<b>Total (N =111)</b>
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months 95% CI	17.5 (15.8, NR)

CI = confidence interval; CR = complete response, PR = partial response, NR = not reached.

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

From the statistical review:

*In Study PCYC-1104-CA, the overall response rate (ORR) was 65.8% (95% CI [56.2%, 74.5%]) with median duration of response (DOR) of 17.5 months (lower 95% confidence limit (CI) of 15.8 months, and upper 95% CI not evaluable).*

*Study PCYC-1104-CA was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.*

*The response data from PCYC-1104-CA demonstrate durable treatment effect of ibrutinib for relapsed and refractory mantle cell lymphoma patients.*

I agree with the conclusions of the clinical and statistical review team. I also agree with the recommendations for accelerated approval based on the submitted data. In particular this applicant has chosen to use a revision of response criteria that has been used for prior Velcade and Revlimid applications. The following text from the primary reviewer and CDTL reviews discuss the issue:

- The ibrutinib NDA represents the first regulatory application of the 2007 Response Criteria for a MCL indication. The MCL approvals for Revlimid and Velcade were based on the 1999 Response Criteria. A new feature in the 2007 Response Criteria is the integration of FDG-PET scans in the response assessments. Patients were not followed long enough to correlate FDG-PET scan determination of response with long-term outcomes. Whether the FDG-PET-negative complete responses confer the same benefit as CT-based complete response is unknown. There is also limited information in the published literature on the long-term outcomes of patients with MCL assessed using the 2007 Response Criteria, and even less information on patients with MCL treated with targeted therapy, such as ibrutinib.*

- *FDG-PET scans were considered exploratory in the Revlimid trial, and were conducted in 25% of the patients. FDG-PET scans were not mentioned in the Velcade trial. In contrast, 100% of patients had FDG-PET scans at baseline in the ibrutinib trial, and the protocol required mandatory FDG-PET scans for documentation of complete responses.*

*Eight of the 19 patients who achieved a CR based on the 2007 criteria would not be considered a CR based on the 1999 criteria. A longer duration of follow-up is needed to further characterize the correlation of on-treatment FDG-PET scans with long-term outcomes.*

- *The MCL indication for ibrutinib is not supported by efficacy in any other indications.*
  - *At the time of regular approval for a MCL indication, both Revlimid and Velcade had received regular approval based on data from large randomized, controlled trials (RCTs). Prior to approval for MCL, Velcade had received regular approval for previously treated multiple myeloma based on a RCT (N=669) that showed a significant effect on time to progression (TTP) (HR 0.55, P<0.001) and OS (HR 0.57, P<0.05). Prior to approval for MCL, Revlimid had received approval for the treatment of patients with previously treated multiple myeloma based on the results of 2 large RCTs (N=353 and N=351), and both trials showed significant improvements in TTP [hazard ratio (HR) 0.285 and 0.324, P<0.001 for both trials].*

*Because multiple therapies are now approved for mantle cell lymphoma, it is important to comprehensively characterize the efficacy of antineoplastic agents and the disease course and to determine adequacy of long-term follow-up. Therefore, this reviewer does not recommend the use of the same approval standard for Revlimid and Velcade for future approvals for mantle cell lymphoma. Important questions for mantle cell lymphoma treatment remain, such as, optimal use of combination treatment regimens, comprehensive characterization of the disease course (nodal and extranodal sites), and evaluation of the treatment effect on time-to-event endpoints including progression-free survival and overall survival.*

*The regular approval of Revlimid and Velcade occurred at a time when there was limited available therapy. Standards for approval for drugs used in the treatment of mantle cell lymphoma may need to be reconsidered. This approach would be consistent with the regulatory history for approvals for cutaneous T-cell lymphoma (CTCL). The initial regular approvals for CTCL (Zolinza and Istodax) were based on single-arm trials. With the availability of these therapies, FDA now recommends randomized controlled trials for future approvals for CTCL, and this approach was also supported by ODAC. The most recent regular approval for CTCL, Valchlor (topical nitrogen mustard), was based on the results of a randomized controlled trial.*

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

## **8. Safety**

The following text is from the CDTL review:

### **Safety Summary**

*The safety profile of ibrutinib was primarily evaluated in 111 patients with previously treated MCL enrolled in PCYC-1104-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 starting ibrutinib dose was 560 mg once daily. The median duration of ibrutinib treatment with ibrutinib was 8.3 months (range 0.7 to 21.4+ months). At the time of data cut-off, 46 patients remained on therapy.*
- *There were 16 deaths within 30 days of treatment with ibrutinib (8 deaths due to disease progression, and 8 deaths due to treatment-emergent adverse events). The deaths due to adverse events include 2 cases of pneumonia and 1 case each of sepsis, respiratory failure, acute renal failure, paralytic ileus, cardiac arrest, and dyspnea.*
- *There were 62 patients (55.8%) who experienced serious adverse events (SAEs). Infection was the most common SAE.*
- *Discontinuations due to TEAEs occurred in 9 patients (8.1%).*
- *Almost three quarters of subjects (74%) experienced a Grade 3 or Grade 4 treatment-emergent adverse event (TEAE). Neutropenia, thrombocytopenia, anemia, and pneumonia were the most common Grade 3 and 4 TEAEs.*
- *TEAEs that occurred in  $\geq 20\%$  of patients include thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.*
- *No new safety signals were detected in the analysis of 120-day safety update data.*
- *Review of the adverse events of special interest revealed the following:*
  - *Hemorrhagic events (MedDRA 15.1 SMQ Hemorrhage terms [excluding laboratory terms]) occurred in 48% of the patients. Major bleeding events occurred in 7 patients (6.3%). Two subjects had grade 3 subdural hematoma, one had grade*

*2 and one had grade 1 subdural hematoma. Two subjects had grade 3 hematuria and one had grade 3 lower gastrointestinal hemorrhage. The majority of the hemorrhagic events were grade 2 or less, with bruising and ecchymoses as the most common hemorrhagic events.*

*The mechanism for the bleeding events is not well understood. There was no correlation between thrombocytopenia and the occurrence of bleeding events.*

- *Second primary malignancies occurred in 5% of patients with MCL, including skin cancers (4%) and other carcinomas (1%).*
- *Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%).*
- *Infections occurred in 82 (74%) patients. At least 25% of patients with MCL had CTCAE Grade 3 or greater infections.*
- *Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients.*
- *Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.*

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.

From the IRT review for the potential for QT prolongation:

*For the objective of a dedicated QTc assessment following treatment with ibrutinib, we conclude that the current QTc study is inconclusive due to the following limitations in trial design:*

*Baseline ECGs were not adequately collected. The Sponsor used screening ECGs that were collected at any time point up to two weeks before the drug was administered.*

*Single on-treatment ECGs were collected in this study. Triplicate ECGs should be collected to reduce variability in QT measurements.*

*In a previous review (1/30/13), QT-IRT recommended that a thorough QT study be conducted for ibrutinib and the results be submitted as a post-marketing requirement. After reviewing the current study we reaffirm our previous recommendation.*

I concur with their recommendation.

## 9. Advisory Committee Meeting

This application is the third submitted within the past 10 years for an indication to treat mantle cell lymphoma. 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 – in section 7 above see discussion of reasons for accelerated approval.

- Risk Benefit Assessment

MCL remains an incurable disease at this time with few available treatment options. 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

Enhanced pharmacovigilance in order to characterize bleeding risks in patients treated with Imbruvica including their potential association with concomitant use of anti-platelet and/or anticoagulant drugs

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 – The first requirement will involve the submission of longer term follow-up from the single arm trial (PCYC-1104-CA) and the second requirement will involve the submission of the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma.

There will be additional PMRs that involve the following:

1. Determination of the effect of a broad range of concentrations of ibrutinib on platelet function by in vitro studies
2. Submission of the final study report for the hepatic impairment trial PCI-32765CLL1006
3. Submission of the final study report for trial PCI-32765CLL1010 to assess the effect of Rifampin on the Pharmacokinetics of ibrutinib.

(b) (4)

There will be a PMC that addresses the dissolution profile of ibrutinib under various conditions.

-----  
**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  
11/08/2013