CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s000

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
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 mantle cell lymphoma (MCL) who have received at least one prior therapy
Recommended:	Approval

Material Reviewed/Consulted	Reviewer
Clinical Review	Karen McGinn, M.S.N., C.R.N.P. / 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 proposed for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Imbruvica (ibrutinib) is a new molecular entity and 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-1104-CA, an open-label, single-arm trial of ibrutinib monotherapy in 111 patients with MCL who have received at least one prior therapy. Clinical trials of ibrutinib in MCL and other hematologic malignancies are in progress.

2. Background

Mantle cell lymphoma (MCL) represents approximately 6-7% of all new Non-Hodgkin Lymphoma (NHL) cases per year. The estimated incidence of MCL is 0.51 to 0.55 cases per 100,000 persons in the US. MCL is more common in males, 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. Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes due to the incurability of the disease with conventional chemotherapy and a more aggressive disease course.

There is no curative therapy for MCL with the exception of rare patients who achieve long-term, disease-free survival after allogeneic stem cell transplantation. The median overall survival in patients with newly-diagnosed MCL is 3 to 4 years, with no plateau in the survival curve. First-line treatment regimens include multi-agent chemotherapy regimens; however, almost all patients will eventually relapse.

The prognosis for patients with relapsed MCL is poor. Velcade and Revlimid are the only FDA-approved treatments for patients with MCL who had received at least 1 prior therapy. The Velcade approval (2006) was based on a single-arm clinical trial of Velcade monotherapy in 155 patients with progressive MCL who had received at least 1 prior therapy, and demonstrated 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 (2013) was based on a single-arm clinical trial of Revlimid monotherapy in 134 patients who have relapsed or were refractory to bortezomib or a bortezomib-containing regimen, and demonstrated the following results: ORR 26%, CR 7%, and median DOR of 16.6 months.

3. CMC/Device

- General product quality considerations

Drug Product. Ibrutinib is being co-developed by Pharmacyclics, Inc. (Pharmacyclics) and Janssen Research & Development, LLC (Janssen R&D). The drug product is an immediate-release opaque white size 0 hard gelatin capsule for oral administration, containing 140 mg of ibrutinib drug substance and commonly used compendial excipients such as microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate, etc. The drug product is packaged in two configurations: 160 cc HDPE bottles with (b) (4) child-resistant closure containing 90 capsules and 200 cc HDPE bottles containing 120 capsules.

The drug product is manufactured by the contract manufacturer, (b) (4) The intended commercial scale is (b) (4) capsules (b) (4) total weight). Manufacturing of Ibrutinib Capsules uses (b) (4)

The drug product specifications consist of description, identity, assay, individual and total degradation products, (b) (4) content uniformity, dissolution and microbial limits. The HPLC method used for identity, assay and content uniformity is the same method that is used for the drug substance assay. The acceptance limits for the three identified degradation products have been qualified and/or below the safety threshold for oncology drugs per the pharmacology-toxicology review team. The acceptance limits for degradation products (b) (4) have been tightened per FDA's comments.

Stability studies for drug product were performed. Stability data for 3 registration batches, 7 primary stability batches and one supportive stability batch were submitted. The drug product appears to be fairly stable. Only a slight increasing trend of degradation products (b) (4) and a slight decreasing trend of assay have been observed. Up to 24 months long term primary and supportive stability data are well within the specification. Six months of accelerated stability data also conform to the specification with a clearer trending for degradation products and assay value. Photostability study conducted per ICH guidelines showed that the drug product is not light sensitive. Based on the primary and supportive stability data the shelf life of 24 months stored at "storage temperature at 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)" can be granted.

Drug Substance. The drug substance is Ibrutinib. The chemical name is 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo [3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one. It has a molecular formula of C25H24N6O2 and its molecular weight is 440.50.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route (b) (4) are adequate for the manufacturing of the ibrutinib drug substance.

The impurities detected during the development and synthesis of the drug substance were evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was adequately presented.

Ibrutinib was subjected to heat, heat and moisture, light, and chemical stresses. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retest period of (b) (4) months.

Biopharmaceutics. ONDQA-Biopharmaceutics had reviewed the information provided in NDA 205-552 for Ibrutinib (PCI-32765, JNJ 54179060) 140 mg hard gelatin capsules. The proposed SLS dissolution method QCM-164 and acceptance criterion of Q = (b) (4) at 30 minutes are acceptable on an interim basis. The final dissolution method and acceptance criterion for Ibrutinib capsules will be implemented after the dissolution information/data to be collected under the PMC is evaluated and approved.

Product Quality Microbiology. The Microbial Limits specification for Ibrutinib 140 mg Capsules is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

- Facilities review/inspection: Acceptable

- Other notable issues (resolved or outstanding): None

Overall Conclusion from Tertiary CMC Review (Ramesh Sood, Ph.D., 10/4/13)**:** The final recommendation from the Office of Compliance (OC) is pending at the time of writing this memorandum. All CMC related issues have been resolved. The application is recommended for "Approval" from CMC perspective pending overall "Acceptable" recommendation from OC. A memorandum with final overall recommendation will be entered into DARRTS after the OC recommendation.

CMC Review Addendum (10/21/2013)**:** From a CMC perspective, this application is recommended for Approval. EES has an overall "Acceptable" recommendation for this NDA.

4. Nonclinical Pharmacology/Toxicology

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

  Ibrutinib is a small molecule tyrosine kinase inhibitor developed for the treatment of mantle cell lymphoma (MCL) [redacted] (b) (4) Ibrutinib inhibits Bruton tyrosine kinase (Btk), an enzyme in the B cell receptor (BCR) signaling pathway. Btk is involved in B-lymphocyte activation and in the maintenance of some B-cell malignancies. Based on an in vitro kinase assay conduced, ibrutinib can also inhibit Bmx/Etk, another member of this kinase family, the function of which is not fully understood. It can also inhibit EGFR, and some members of the SRC family of kinases (e.g. Hck and Yes); however, with up to 10 fold less activity. In xenograft and/ or cell culture studies, ibrutinib showed anti-cancer activity against cells derived from B-cell malignancies, including MCL and CLL lines. Ibrutinib inhibited the adhesion of MCL and CLL cells to fibronectin and vascular cell adhesion molecule-1 (VCAM-1), suggesting the potential for ibrutinib to affect the trafficking of B-cells.

  Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in in vitro systems and/or in animal species. Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Ibrutinib-related toxicities in rats and dogs included: GI toxicities (e.g. ulceration and inflammation), adverse findings in the lymphoid tissues (e.g. depletion, necrosis, and inflammation), and epidermal necrosis and exudate. Other findings with unknown association to treatment included muscle degeneration in the stomach, effects on bone (e.g. thinning of cortical bone), and pancreatic acinar atrophy/ reduced zymogen granules.

- Carcinogenicity

  Ibrutinib was not mutagenic or clastogenic when tested in the battery of genotoxicity studies. Several impurities were tested in the bacterial mutagenicity (Ames) assay and/or assessed for mutagenicity through SAR (structure- activity relationship) computational methods. The impurities were considered negative for mutagenicity. Ibrutinib caused fetal malformations in rats when given to pregnant animals during the period of organogenesis, at a maternally toxic dose. Pregnancy category D is recommended.

- Reproductive toxicology

  Fertility studies using ibrutinib have not been conducted. The general toxicology studies in rats and dogs did not demonstrate adverse findings in male or female reproductive organs.

- Other notable issues (resolved or outstanding)

  None

Overall Conclusion from Tertiary Pharmacology-Toxicology Review (John Leighton, Ph.D., DABT): I have examined pharmacology/toxicology supporting review for ibrutinib conducted by Drs. Lee, Chiu, Brower and Chang, and secondary memorandum and labeling provided by Dr. Saber. I concur with Dr. Saber's conclusion that ibrutinib may be approved and that no additional nonclinical studies are needed for the proposed indication.

5. Clinical Pharmacology/Biopharmaceutics

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

  Ibrutinib is an irreversible Bruton's tyrosine kinase (BTK) inhibitor that binds to a cysteine residue (Cys-481) in the BTK active site. The applicant proposes oral dosing regimen of 560 mg once daily in MCL. Pharmacokinetic data to support the clinical pharmacology program were submitted from the pivotal MCL trial and three additional trials (mass balance trial, CYP3A4 inhibitor trial and a dose-escalation trial).

  Ibrutinib exposure increases with doses up to 840 mg. The median ibrutinib Tmax ranged from 1 to 2 hours and the mean elimination half-life ranged from 4 to 6 hours. The mean accumulation ratio observed at steady state ranged from 1 – 1.6. In a food effect cohort (sub-study) of trial 1102-CA, a high-fat meal increased ibrutinib exposure approximately 2-fold compared to when ibrutinib was administered after an overnight fast. In an oral mass balance trial, radioactivity recoveries in feces and urine were 81% (<1% unchanged ibrutinib) and 8%, respectively. The absolute bioavailability of ibrutinib has not been determined.

- Drug-drug interactions and Pathway of elimination

  Ibrutinib is extensively metabolized and is primarily metabolized by CYP3A4. In a dedicated drug-interaction trial, concomitant ketoconazole (strong CYP3A4 inhibitor) increased ibrutinib Cmax 29-fold and AUC 24-fold. Based on preliminary clinical trial data and PBPK modeling, concomitant rifampin (strong CYP3A4 inducer) decreased the Cmax and AUC of ibrutinib by 14-fold and 13-fold, respectively. PBPK modeling predicted that moderate CYP3A4 inhibitors can increase ibrutinib exposure 6 -9 fold and mild inhibitors can increase ibrutinib exposure 2 fold. In addition, a moderate inducer is predicted to decrease ibrutinib exposure 3-fold.

- Intrinsic and extrinsic factors

  Hepatic impairment increases ibrutinib exposure. Preliminary data from an ongoing Trial PCI-32765CLL1006 in patients with moderate hepatic impairment (Child-Pugh B; N=3) shows a 6 fold increase in exposure when compared to mean exposures in patients with normal hepatic function.

  A dedicated renal impairment trial has not been conducted. Approximately 8% of radioactivity was detected in urine in the mass balance trial suggesting that the renal route is a minor elimination pathway.

  Weight had no meaningful influence on the clearance of ibrutinib, but had influence on volume of distribution. This influence on volume of distribution does not seem to have any meaningful impact on the exposure to ibrutinib.

  In the mass balance trial (n = 6), CYP2D6 poor metabolizers (PM; N=2) did not appear to have an increase in ibrutinib or PCI-45227 exposure compared to extensive metabolizers (EM; N=4).

  The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for ibrutinib were not assessed in a formal study.

- Exposure-response

  No exposure-response relationships for effectiveness or safety were observed in the dose range of 420 - 840mg. Dose-response relationship for BTK occupancy and clinical response in the phase 1 dose escalation trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg).

- QT assessment

  The IC_{50} for inhibitory effect by ibrutinib on hERG channel current was 970 nM (427 ng/mL) and was 9600 nM (4229 ng/mL) for PCI-45227 (active metabolite). The non-clinical reviewer commented that ibrutinib can be considered a low-potency blocker of the hERG channel.

  A formal thorough QT trial has not been performed for ibrutinib. Formal ECG monitoring was performed in 2 single-arm trials (PCYC-04753 [n = 45] and PCYC-1102-CA [n = 67]). The QT-IRT evaluated the relationships between Δ QTcF and ibrutinib and PCI-45227 concentrations and did not observe an exposure-response relationship. QT-IRT has concluded that the submitted QTc data is inconclusive due to the following limitations in trial design: (1) baseline ECGs were not adequately collected, and (2) only single on-treatment ECGs were collected (triplicates

recommended). The applicant had used screening ECGs that were collected at any time point up to two weeks before the drug was administered.

The QT/IRT is not proposing any labeling language and a PMR will be issued for the applicant to perform and submit the results of a thorough QT trial. The protocol for this trial was previously submitted and reviewed by QT-IRT. The applicant has stated that they plan to perform the trial in 2014.

- Other notable issues (resolved or outstanding): Refer to Section 13 for post-marketing requirements.

Overall Recommendation from Clinical Pharmacology (11/1/2013)**:** The Office of Clinical Pharmacology Divisions of Clinical Pharmacology V, Pharmacometrics and Genomics have reviewed the information contained in NDA 205-552. This NDA is acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 3 for product quality microbiology information.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the statistical reviewer (Dr. Yun Wang) and clinical reviewer (Karen McGinn) for the efficacy of ibrutinib for patients with MCL 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-1104-CA (single-arm trial in patients with MCL) was initiated on October 13, 2010. End of Phase 2 (EOP2) meetings to discuss the MCL clinical development program including registrational approach occurred on March 7, 2012 and December 3, 2012. Fast Track was granted for the treatment of patients with relapsed or refractory MCL on December 18, 2012. On February 8, 2013, Breakthrough Therapy designation was granted by the FDA for the treatment of patients with relapsed or refractory MCL based on review of topline results of clinical trial PCYC-1104-CA. Pre-NDA meeting occurred on March 29, 2013.

The Applicant's MCL clinical development program for ibrutinib includes other ongoing or planned clinical trials (Refer to Table 1).

Table 1. Applicant's ongoing clinical trials of ibrutinib in MCL (Source: Applicant's Clinical Overview M2.5, page 16)

Study Number (Study Phase)	Study Design \ Study Population \ Study Treatment	No. Subjects Planned and Enrolled[a] Target Enrollment Completion Date
PCI-32765MCL2001 (Phase 2)	Open-label, single-arm, multicenter; subjects with MCL who have received ≥1 rituximab-containing regimen and progressed after receiving ≥2 cycles of bortezomib therapy; evaluate ORR.	Planned: (b) (4) Enrolled: Apr 2013
PCI-32765MCL3001 (Phase 3)	Randomized, controlled, open-label, multicenter; subjects with relapsed/ refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen; evaluate efficacy and safety of ibrutinib vs. temsirolimus.	Planned: (b) (4) Enrolled: 1Q 2014
PCI-32765MCL3002 (Phase 3)	Randomized, double-blind, placebo-controlled, multicenter; subjects with newly diagnosed MCL who are 65 years or older; evaluate efficacy and safety of ibrutinib in combination with bendamustine and rituximab (BR) vs. BR alone in subjects with newly diagnosed MCL.	Planned: 520 Enrolled: 0 3Q 2014

ORR: overall response rate;
[a] Enrollment as of the cutoff date of 01 May 2013.

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 ≥ 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

	Total (N =111)
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%.

Primary Reviewer Conclusions
The statistical reviewer concluded that PCYC-1104-CA demonstrated durable overall response benefit of ibrutinib for patients with mantle cell lymphoma who received at least one prior regimen.

The clinical reviewer concluded that the Applicant has demonstrated the efficacy of ibrutinib in patients with mantle cell lymphoma (MCL) who have been previously treated. The objective response rate (ORR) was 65.8% and median duration of response (DOR) was 17.5 months in Trial PCYC-1104-CA.

8. Safety

I concur with the clinical reviewer's (Karen McGinn) conclusions regarding the safety of ibrutinib.

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 ≥ 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 occurred 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..

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

Ibrutinib is exempt from the pediatric study requirements in 21 CFR 314.55. Ibrutinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of MCL on 3 December 2012. Ibrutinib 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 arose with respect to possible bias arose from the large monetary donations to the two sites with the largest enrollment into Trial [redacted] which enrolled [redacted] of the [redacted] evaluable subjects and [redacted] which enrolled [redacted] of evaluable subjects. 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-1104-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 17 subjects who were screened and 14 subjects who were enrolled. A 100% verification of the informed consent documents of the enrolled subjects was done.

  A complete audit of 14 subjects' records was conducted. 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 for the clinical investigation sites.

  In addition, the Applicant was inspected and was evaluated for the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors. In general, the Applicant maintained adequate oversight of clinical trial PCYC-1104-CA.

  The overall conclusion from OSI states that clinical trial PCYC-1104-CA appears to have been conducted adequately and the data generated appear acceptable in support of the 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.** OSE/DPV recommended an enhanced pharmacovigilance plan for hemorrhagic events. Refer to Section 13 for the agreed upon post-marketing requirement with the Applicant**.**

  Pre-marketing clinical trials with ibrutinib identified hemorrhagic adverse events as a safety concern. Both major and minor hemorrhagic events were seen in clinical trials, although the risk of these events is not fully understood due to the limited number of subjects enrolled in clinical trials. Major hemorrhagic events included gastrointestinal bleed, cranial hemorrhage, and hematuria. Minor hemorrhagic events included bruising, epistaxis, and petechiae. A description of hemorrhagic events with ibrutinib will be conveyed in the product label under Warnings and Precautions. However, the safety concern of hemorrhage with ibrutinib remains an important identified risk that requires further evaluation.

- **OSE/DRISK.** Based on the information that is currently available, a REMS with a communication plan or elements to assure safe use for ibrutinib is not recommended. Implementing a REMS for ibrutinib without a better understanding of factors that may contribute to the risk of bleeding may restrict therapy without evidence establishing who is at increased risk for bleeding events, and may create a barrier that prevents patients who could benefit from the drug from receiving it. It would not be appropriate to exclude all patients with risk factors for bleeding from receiving ibrutinib until additional data are available to better understand the bleeding safety signal. A communication plan REMS would not be helpful because there is not a clear message to communicate to prescribers. Better understanding of factors that contribute to increased risk of bleeding are needed to create an effective risk message.

- **OSE/DMEPA.** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

- **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 MCL is a serious and life-threatening illness with an overall poor prognosis. The efficacy and safety results in clinical trial PCYC-1104-CA demonstrate an acceptable benefit-risk profile for ibrutinib for the treatment of patients with previously treated MCL. All review team members recommend approval.

  However, although ibrutinib showed a high level of activity (ORR 66% including 17% CR rate) and median DOR of 17.5 months, the following issues in the efficacy evaluation were observed which would be more supportive of accelerated approval as compared to regular approval. Refer to the primary clinical review for a detailed discussion.

  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.

  - There is uncertainty as to the relation of ORR and DOR to ultimate outcome (overall survival). In the trial, although the ORR was 66% and the median DOR was 17.5 months, 48% of the patients experienced progressive disease, and 30% of the patients in the trial died due to progressive disease.

  - The median DOR is based upon a small number of events with limited follow-up duration. The estimated median DOR of 17.5 months is primarily determined by only 4 patients who have reached that timepoint. Fifty-six percent (28/50) of the patients censored for DOR had less than 12 months of follow-up.

  - Quantitative response assessments did not include extra-nodal sites of disease despite more than half of the patients (54%) having extra-nodal disease. In addition, the clinical significance of treatment-emergent lymphocytosis is unknown. Whether lymphocytosis contributes to seeding of extranodal sites that may later lead to disease progression is also unknown.

  - 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.

- The MCL indication for ibrutinib is not supported by efficacy in any other indications.

CDTL Recommendation: Because multiple therapies are now approved for mantle cell lymphoma, it is important to adequately characterize the efficacy of agents, including comprehensive characterization of the disease course and adequate long-term follow-up. The regular approval of Revlimid and Velcade occurred when there was no or limited available therapy.

The standards for approval of drugs for the treatment of mantle cell lymphoma require reconsideration. 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, the FDA has recommended randomized controlled trials for future approvals for CTCL. 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.

For this application, I recommend accelerated approval due to the limitations in the efficacy results listed above, and advocate for the completion of the Subpart H PMRs to adequately characterize the efficacy of ibrutinib for the treatment of mantle cell lymphoma.

- 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 ibrutinib.

- Recommendation for other Postmarketing Requirements and Commitments

I agree with the following postmarketing requirements and commitments proposed by the review teams, and agreed upon with the Applicant. PMR 2060-1 and 2060-2 are efficacy PMRs (Subpart H). PMRs 2060-3 to 2060-7 represent safety PMRs. PMR 2060-8 is a CMC PMC for the dissolution profile.

PMR 2060-1: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression. Summarize extranodal disease characteristics at baseline and at time of progression. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression.

Final Protocol Submission:	Completed 01/2013
Trial Completion:	09/2014
Final Report Submission:	03/2015

PMR 2060-2: Complete and submit 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. Enrollment of approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.

Final Protocol Submission:	Completed 04/2013
Trial Completion:	12/2018
Final Report Submission:	03/2019

PMR 2060-3: Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

Draft Protocol Submission:	06/2014
Final Protocol Submission:	12/2014
Study Completion:	06/2016
Final Report Submission:	12/2016

PMR 2060-4: Perform enhanced pharmacovigilance for clinical trials and all post-marketing sources in order to characterize bleeding risks in patients treated with Imbruvica ®, PCI-32765 (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events (defined below) and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs.

(b) (4)

(b) (4)

The definition of a major hemorrhagic event includes any one of the following:

I. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
II. Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells,
III. Bleeding resulting in a serious adverse drug experience [as per 21 CFR 314.80(a)]

The enhanced Pharmacovigilance Plan includes:

1. Targeted and expedited surveillance with a guided collection form (as referenced in Pharmacyclics' Pharmacovigilance Plan dated August 23, 2013) to obtain additional salient clinical and diagnostic information related to major hemorrhagic events.

2. Submission of Post-marketing 15-day Alert Reports (b) (4) of all initial and follow-up reports of serious hemorrhagic adverse events from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports, utilizing the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) – Haemorrhages. (b) (4)

3. Submission of interval and cumulative analyses, and line listing for all major hemorrhagic events utilizing the SMQ Haemorrhages from clinical trials and all post-marketing sources, including consumer reports, solicited reports, and foreign reports (b) (4)

(b) (4)

(b) (4)

4. Analysis of potential risk factors for cumulative major hemorrhagic events identified from both clinical trials and all postmarketing sources, and an overall assessment about these events in patients treated with Imbruvica®, PCI-32765 (ibrutinib) Capsules.

5. In your submissions, please comment on whether the data warrants further detailed assessment, labeling changes and/or other communication about these adverse events. (b) (4)

Draft Protocol Submission:	12/2013
Final Protocol Submission:	03/2014
#1 Interim Report Submission	06/2014
#2 Interim Report Submission	12/2014
#3 Interim Report Submission	06/2015
#4 Interim Report Submission	12/2015
#5 Interim Report Submission	06/2016
#6 Interim Report Submission	12/2016
#7 Interim Report Submission	06/2017
Study Completion:	11/2017
Final Report Submission:	05/2018

PMR 2060-5: Evaluate the effect of hepatic impairment on ibrutinib PK. Submit the final report for trial PCI-32765CLL1006 entitled, "An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects With Varying Degrees of Hepatic Impairment".

Final Protocol Submission:	Completed 11/2012

Trial Completion: 06/2014
Final Report Submission: 12/2014

PMR 2060-6: Determine effect of a strong CYP3A Inducer on Ibrutinib PK. Submit the final 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".

Final Protocol Submission: Completed 01/2013
Trial Completion: Completed 01/2013
Final Report Submission: 04/2014

PMR 2060-7: Determine the effect of Ibrutinib on the QT/QTc interval in healthy subjects on one or more therapeutic dose levels. Conduct and submit results of a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval.

Draft Protocol Submission: 03/2014
Final Protocol Submission: 06/2014
Trial Completion: 06/2015
Final Report Submission: 12/2015

PMC 2060-8: Collect additional dissolution profile data (n=12 at release and n=12 on stability) using USP Apparatus Type 2 (Paddle) at 75 rpm in 3.0% w/v polysorbate 20 (Tween® 20) in 50 mM phosphate buffer pH 6.8 at 37.0°C from at least ten drug product release batches and from the drug product stability-registration/ primary batches through 12 months of storage at the long-term condition. Use the overall dissolution data that were collected from the drug product's release and stability batches to set the final dissolution acceptance criteria.

Study Completion: 11/2014
Final Report Submission: 02/2015

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

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

/s/

ROMEO A DE CLARO
11/08/2013