CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	205552
Applicant Name	Pharmacyclics, Inc.
Date of Submission	28 June 2013
PDUFA Goal Date	28 February 2014
Proprietary Name / Established (USAN) Name	Imbruvica/ ibrutinib
Dosage Forms / Strength	Capsules, 140 mg
Proposed Indication(s). See approved labeling for final approved indication.	Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Action:	*Accelerated Approval*

Material Reviewed/Consulted: OND Action Package, including:	
	Names of discipline reviewers
Division Director Review	Ann Farrell
Regulatory Project Manager Review	Diane Hanner
Medical Officer Review	Karen McGinn
Statistical Review	Yun Wang, Lei Nie
Pharmacology Toxicology Review	Shwu-Luan Lee, Haw-Jyh (Brian) Chiu, George Ching-Jey Chang, Margaret E. Brower, Haleh Saber, John Leighton
CMC/ONDQA Reviews	Xiao Hong. Chen, Donghao Lu, Janice Brown, Ramesh K. Sood, Ali Al-Hakim, John Z. Duan, Angelica Dorantes
Microbiology Review	Brian Riley, Stephen Langille
Clinical Pharmacology Review	Elimika Pfuma, Julie Bullock, Rosane Orbach, Bahru Habtemariam, Anshu Marathe, Ping Zhao
OPDP Reviews	Nisha Patel, Karen Rulli
OSI Review	Anthony Orencia, Janice Pohlman, Kassa Ayalew
CDTL Review	R. Angelo de Claro
OSE/DPV	Katherine Coyle, Tracy Salaam
OSE/DMEPA Consult	Kevin Wright, Yelena Maslov, Carol Holquist
OSE/DRISK Consult	Joyce Weaver, Cynthia LaCivita
Maternal Health Consult	Karen Dowdy, Nisha Patel, LaShawn Griffiths, Barbara Fuller

OND=Office of New Drugs
CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology
OPDP= Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI= Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DRISK=Division of Risk Management
DMEPA= Division of Medication Error Prevention and Analysis

1 Regulatory Action

The Division of Hematology Products is recommending accelerated approval of Imbruvica® (ibrutinib) Capsules, 140 mg, for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. I concur with their recommendation for accelerated approval under 21 CFR 314.510.

2 Introduction

Pharmacyclics submitted a New Drug Application (NDA) 205552 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Imbruvica®, PCI-32765 (ibrutinib) Capsules, 140 mg. Ibrutinib is a new molecular entity and first-in-class Bruton's tyrosine kinase inhibitor (Btk) that targets B-cell antigen receptor (BCR) signaling pathway. Btk is involved in B-lymphocyte activation and in the maintenance of some B-cell malignancies. In xenograft and/or cell culture studies, ibrutinib showed anti-cancer activity against cells derived from B-cell malignancies, including MCL and CLL lines. The application was filed as a priority review. Ibrutinib received Breakthrough Therapy Designation on February 8, 2013 for treatment of patients with relapsed or refractory MCL based on review of topline results of clinical trial PCYC-1104-CA.

Pharmacyclics proposed the indication of "the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy." The application is supported by a single clinical trial PCYC-1104-CA, which is 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 (Table 1) and other hematologic malignancies are in progress.

Table 1: Pharmacyclics ongoing clinical trials of ibrutinib in patients with mantle cell lymphoma (MCL).

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.

3 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, however, 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 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 in 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 in 2013 was based on a single-arm clinical trial of Revlimid monotherapy in 134 patients who relapsed after 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.

4 CMC/Biopharmaceutics

There are no issues that preclude approval for CMC/biopharmaceutics. CMC reviewers have provided an overall acceptability for the manufacturing of drug product and drug substance.

Biopharmaceutics PMC: collect additional dissolution profile data (release and on stability) using the same USP Apparatus Type 2 (Paddle) at 75 rpm in a different dissolution medium from that described in the NDA.

5 Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval for nonclinical pharmacology/toxicology.

Pregnancy category D is recommended based on findings of fetal malformations in rats when given to pregnant animals.

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. Gastrointestinal, skin, and musculoskeletal disorders have been reported in patients and are listed in the label.

6 Site Inspections

Following inspection of two US clinical investigation sites, OSI states that the data from clinical trial PCYC-1104-CA can be relied on.

7 Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

Ibrutinib is extensively metabolized in the liver and is primarily metabolized by CYP3A4. 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. 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. Drug-drug interactions with moderate CYP3A inhibitors and strong CYP3A inducers are also anticipated based on preliminary clinical trial data and the approved labeling reflects this. Therefore, further characterization of a strong CYP3A inducer and evaluation of the effect of hepatic impairment on ibrutinib pharmacokinetics will be assessed in two PMRs.

A formal thorough QT trial has not been performed for ibrutinib. Review of the submitted ECG data is inconclusive. Therefore, a thorough QT study is recommended as a PMR.

8 Clinical Microbiology

Not applicable.

9 Clinical/Statistical-Efficacy

This application, supported by the registration trial PCYC-1104-CA, demonstrates substantial evidence of efficacy for ibrutinib for patients with previously treated mantle cell lymphoma (MCL). I concur with the assessment of Drs. McGinn, DeClaro, and Farrell.

The efficacy of ibrutinib was evaluated in an open-label, multi-center, single-arm trial of 111 patients with previously treated MCL. The median age of this population was 68 years, 77% were male, and 92% were Caucasian. The median time from diagnosis to enrollment was 42 months and the median number of prior treatments was 3 with a range of 1 to 5 prior treatments. This population is representative of the population treated in practice.

Tumor response was measured using the revised International Working Group for non-Hodgkin's lymphoma criteria. The primary efficacy endpoint was investigator-assessed overall response rate (complete response + partial response) and the results are shown in Table 2. An independent review committee performed an independent reading of the imaging scans with a comparable resultant ORR of 69%.

Table 2: Overall response rate (ORR) and duration of response based on investigator-assessment in patients with MCL.

	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
DOR = duration of response; NR = not reached.

10 Safety

The safety profile of ibrutinib was primarily evaluated in the 111 patients with previously treated MCL enrolled in PCYC-1104-CA and is adequate to characterize the safety profile for the purpose of informing risk-benefit.

The starting dose of ibrutinib in PCYC-1104-CA was 560 mg once daily. The median duration of ibrutinib treatment was 8.3 months (range 0.7 to > 21 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. Serious adverse events occurred in 56% of the patients with infection being the most common.

Treatment emergent adverse events that occurred in ≥ 20% of patients included thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.

Adverse events of special interest for ibrutinib included hemorrhage and secondary primary malignancy. Hemorrhage occurred in 48% of the patients. Major bleeding events occurred in 7 patients (6%). 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. Second primary malignancies occurred in 5% of patients, including skin cancers (4%) and other carcinomas (1%).

Serious hemorrhage adverse events occurred in patients receiving concomitant anticoagulants in the development program of ibrutinib. Pharmacyclics excluded patients taking anticoagulants from all subsequent trials in their development program including PCYC-1104-CA. A significant incidence of thrombocytopenia and hemorrhage events occurred despite this mitigation. Therefore, there are postmarketing requirements to address this issue--see action letter.

11 Advisory Committee Meeting

This application was not referred to ODAC because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

12 Pediatrics

Ibrutinib is exempted from the pediatric study requirements under 21 CFR 314.55. Ibrutinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of MCL on December 3, 2012. Ibrutinib has not been evaluated in pediatric patients.

13 Labeling

- Proprietary name. On 16 August 2013, OSE/DMEPA concluded that the proposed proprietary name, Imbruvica is acceptable.

14 Decision/Action/Risk Benefit Assessment

14.1 Recommended Regulatory Action:

Accelerated approval "For the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy." Imbruvica is being approved based on a surrogate endpoint of response rates in a single-arm trial that is reasonably likely to predict direct clinical benefit.

The first Subpart H Postmarketing Requirement is to extend the duration of follow-up of the patients enrolled in the supporting registration trial, PCYC-1104-CA, and to further characterize the outcome assessment of extranodal disease. Extranodal disease assessment was not assessed in the supporting trial as it is not included in the IWRC criteria. The second subpart H Postmarketing Requirement is to complete and submit the 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 at approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.

14.2 Risk Benefit Assessment

The benefit to risk assessment of Imbruvica® for patients with previously treated Mantle cell lymphoma (MCL) is positive with a high overall response rate of 66% with a median duration of response of 17.5 months.

MCL is a clinically aggressive lymphoma with a poor prognosis. There is a need for additional therapies for patients that have failed first-line treatment. The risk-benefit profile of Imbruvica was discussed in the reviews of Drs. Farrell, De Claro, and McGinn and I concur with their recommendation to grant accelerated approval for this NDA.

14.3 Recommendation for Postmarketing Risk Management Activities: See action letter and discussion of safety PMRs in the Clinical Pharmacology and Safety sections. A REMS to assure safe use of ibrutinib is not recommended.

14.4 Recommendation for other Postmarketing Study Commitments: See action letter.

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

/s/

TAMY E KIM
11/12/2013

RICHARD PAZDUR
11/12/2013