CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 205-552/S-17

Trade Name: Imbruvica

Generic Name: ibrutinib capsules, 140 mg

Sponsor: Pharmacyclics LLC.

Approval Date: August 2, 2017

Indications: For the treatment of patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

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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 #**	205552-017
Applicant Name	Pharmacyclics
Date of Submission	February 2, 2017
PDUFA Goal Date	August 2, 2017
Proprietary Name / **Established (USAN) Name**	Imbruvica/ibrutinib/PCI-32765
Dosage Forms / Strength	140 mg hard gelatin capsules
Proposed Indication(s)	Treatment of patients with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Action/Recommended Action for NME:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Tanya Wroblewski, M.D/R. Angelo de Claro, M.D.
Regulatory Health Project Manager	Esther Park, Pharm.D.
Statistical Review	Kallapa Koti, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Luan Lee, Ph.D. / Christopher Sheth, Ph.D.
CMC Review/OBP Review	Pallaiah Thammana/Ramesh Raghavachari
Microbiology Review	N/A
Clinical Pharmacology Review	Liang Li, Ph.D./Stacy Shord, Ph.D.
DDMAC/OPDP	Nisha Patel/Kathleen Davis/Susan Redwood/Sharon R Mills/LaShawn Griffiths
OSI	Anthony Orencia, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review	Angelo deClaro, M.D.
OSE/DMEPA	Leeza Rahimi, Pharm.D./Yelena Maslov, Pharm. D.
COA Staff	Ebony Dashiell-Aje / Selena Daniels/Elecktra Papadopoulos, M.D.

Signatory Authority Review Template

1. Introduction

On November 13, 2013 Pharmacyclics, Inc. received approval for Imbruvica (ibrutinib). Ibrutinib (PCI-32765) is an irreversible inhibitor of Bruton's tyrosine kinase (Btk). Imbruvica is approved for treatment of patients with the following diseases:

Mantle cell lymphoma (MCL) who have received at least one prior therapy
Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) who have received at least one prior therapy
Chronic lymphocytic leukemia)/Small lymphocytic lymphoma (SLL) with 17p deletion
Waldenströms Macroglobulinemia
Marginal zone lymphoma

This submission provides for a new indication for the treatment of patients with chronic graft versus host disease (cGVHD), which is a serious and life-threatening condition occurring following hematopoietic stem cell transplant.

2. Background

There are no currently approved treatments for chronic graft versus host disease. Corticosteroids are the mainstay for the first-line treatment of cGVHD. There are no approved therapies for the treatment of cGVHD after failure of 1 or more lines of therapy.

From the CDTL review:
The primary basis for the application is clinical trial PCYC-1129-CA, titled "A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease" [Clinicaltrials.gov Identifier NCT02195869].

Formal meetings occurred between the Agency and the Applicant on 3 November 2015 and 31 August 2016 to discuss the development program and registration plans for Imbruvica to support an indication for the treatment of patients with chronic graft-versus-host disease.

FDA granted Breakthrough Therapy Designation for Imbruvica for the treatment of patients with cGVHD after failure of 1 or more lines of systemic therapy on 22 June

2016. Orphan drug designation was granted on 23 June 2016 for ibrutinib for the treatment of chronic graft-versus-host disease….

The Applicant also submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction between a moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A4 inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations.

3. CMC/Device

No issues were identified precluding approval.

4. Nonclinical Pharmacology/Toxicology

No issues were identified precluding approval.

Pharmacology-Toxicology team reviewed the study report for PCYC-1132-NT to address FDAAA 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).*

Findings from PCYC-1132-NT included:

- Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC50 values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively.
- Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Despite the study, the mechanism for bleeding events with ibrutinib remains not well understood.

Based on the above results, PMR 2060-3 is fulfilled.

5. Clinical Pharmacology/Biopharmaceutics

No issues were identified precluding approval. The Applicant submitted the results of a drug interaction trial (PCI-32765LYM1003) that evaluated the potential interaction between a moderate CYP3A inhibitor (erythromycin) and a strong CYP3A inhibitor (voriconazole) in patients with a B-cell malignancy, as well as a summary report of physiologically based pharmacokinetic (PBPK) simulations (16-031-Hu-PO-PBPK) that evaluated the potential interaction between the strong CYP3A4 inhibitor posaconazole and ibrutinib to support changes to the current labeling recommendations. Labeling recommendations were made based on this study and the clinical study in patients with cGVHD.

6. Microbiology

N/A

7. Clinical/Statistical-Efficacy

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

Trial Design
The trial was an open-label, multi-center, single-arm trial of patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. With a sample size of 40 subjects, and an expected overall cGVHD response rate of 50%, the study was expected to have at least 90% power to demonstrate that the lower bound of the 95% confidence interval of the response rate is greater than 25%. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression) to align with the updated 2014 NIH Consensus Panel Response Criteria.

Patient Population
A total of 45 subjects were enrolled, and 43 subjects were treated. The primary analysis population was an all-treated population which included 42 subjects who received at least 1 dose of ibrutinib at the recommended dose of 420 mg once daily, excluding one subject who had evidence of recurrence of underlying malignancy (AML) at the start of study drug.

The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88%) had at least 2

organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily steroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

Efficacy Results

- *The best overall response rate (complete response[CR] + partial response[PR]) was 28/42 (66.7%) [95% CI: (50.5, 80.4)] in the all-treated population. The lower bound of the 95% CI exceeded 25% (the pre-specified threshold of efficacy, $p < 0.0001$); therefore, the primary objective of the study was met.*
- *Nine (21.4%) out of 42 subjects achieved CR and 19 (45.2%) subjects had PR.*
- *The median time to best overall response was 12.3 weeks with a range of 4.2 to 42.1 weeks.*
- *The rate of sustained response in all-treated population for ≥ 20 weeks was 47.6% [95% CI: (32.5, 62.7)].*
- *Median duration of response (DOR) was not reached. DOR for 23 (82%) subjects was censored.*
- *Responses were observed across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).*
- *Eighteen of 42 patients (43%) had at least one LSS summary score measurement that was at least 7 points lower than their baseline LSS score. The percentage of subjects with at least 7 point reduction from baseline in Lee cGVHD symptom Scale score was 60.7% for the responder (17 of 28 subjects) and was 7.1% for the non-responders (1 of 14 subjects) over the duration of the study.*

I agree with the conclusions of the clinical and statistical review team recommending approval for this application.

8. Safety

The most common treatment-emergent adverse drug reactions were fatigue, bruising, diarrhea, muscle spasms, stomatitis, hemorrhage, nausea and pneumonia. Only two new safety issues were identified during the review of this portion of the application: fall and sepsis.

9. Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee meeting because there were no issues with the trial design, conduct, endpoints or data analysis.

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.

The Office of Scientific Investigation review did not uncover serious issues which would interfere with the regulatory use of the data.

12. Labeling

All disciplines made recommendations for labeling. The recommendations were discussed during internal labeling negotiations.

DHP review team requested that the COA staff review the Lee Symptom Scale (LSS), a patient reported outcome measure, which was used as a secondary endpoint in the clinical trial. Office of Hematology and Oncology Products has typically considered placing secondary endpoint information in labeling if the division believed the information could be helpful to the practitioner. The DHP review team decided that information from LSS would be helpful for the practitioner as LSS is used as part of the cGVHD assessment at patient visits. LSS has been in use since initial publication in 2002. Since 2004, publications have referenced the LSS when reporting on cGVHD. The DHP review team consulted the COA staff to understand the potential issues with regard to labeling.

The COA staff did not recommended that the LSS data be placed in labeling and referred to the published PRO guidance. The issues noted are:

1) Whether patient reported data from an open-label single arm trial should be placed in labeling

Single arm, open-label trial design is necessary when enrolling patients who have no alternative treatments and whose condition is not under control. This situation exists for the patients enrolled in the trial described above and whose disease condition is the subject of this application.

Patient reported outcome data from an open-label single arm trial has been placed in approved labeling and has been the primary evidence for the indication.

In 2012 the FDA approved Kineret for "the treatment of *neonatal*-onset multisystem inflammatory disease (NOMID)" based primarily on a single-arm, open-label extension trial using a PRO instrument which included some PROXY reporting due to the median age of patients as patients less than 8 cannot typically report for themselves. The other supporting evidence was laboratory parameter changes. All of the statistics were descriptive.

In Dr. Janet Maynard's Clinical review she wrote:
"..the natural history of NOMID generally involves progressive decline in these domains due to uncontrolled inflammation… while validated outcome measures for NOMID do not exist, the endpoints chosen for Study 03-AR-0298 correspond well to recently agreed standards for assessment of patients with autoimmune disease". "These standards emphasize the assessment of a treatments affect on daily symptoms, acute phase reactants, quality of life, and disease-specific organ inflammation. The primary statistical methods of Study 03-AR-0298 were descriptive. "While this trial was open-label, it was adequate given the marked efficacy of the product and the limitations of evaluating an ultra-rare orphan disease."

Symptoms were collected using the DSSS instrument and calculated as the sum of the severity of five key NOMID symptoms (fever, headache, rash, joint pain, and vomiting). It was recorded daily by the patient or caregiver.

2) Amount of missing data
In Dr. Wroblewski's review of the LSS she notes:

<u>FDA Analysis of the Lee Symptom Scale Results</u>
The clinical review team requested an additional efficacy dataset from the Applicant for the Lee Symptom Scale which include baseline and individual scores for each of the 30 items on the scale. The clinical review team conducted independent analyses of the LSS from the dataset.

Robustness of Data
Overall, there was very little missing data. There were a total of 170 Lee Symptom Scale assessments in 42 patients. There were 26/5100 (0.5%) items missing.

Over time patients did drop out of the study and therefore were not assessable for either the primary endpoint or any secondary endpoints.

3) What does a single time point - seven point improvement on an overall score mean

From Dr. Wroblewski's review:

Lee et al proposed that a 6-7 point decrease (on normalized 1-100 scale) in the LSS overall summary score from baseline. A response in a patient reported outcome could be classified as a response versus no response (no improvement or worsening) as measured by change from baseline and subsequent measurements. The definition or threshold of improvement for the Lee Symptom scale is based on the reliability of the measure. A distribution based analysis was used to define improvement as a change of 6 to 7 points (0.5 standard deviation) on the total chronic GVHD symptom score. For normally distributed data, for patient reported measures a change of 0.5 standard deviation can be considered as clinically meaningful.

Reviewer Comment: The proposed threshold of 6-7 point change based on distribution methods is an acceptable threshold. Future work with the LSS instrument could include anchor-based analyses methods.

The 2014 NIH cGVHD Consensus states that a 0.5 standard deviation may be considered clinically meaningful for normally distributed data and a distribution analysis was used to define improvement as change of 6-7 on the total cGVHD symptom score.

- The original 7 point benchmark was defined by Lee et al. in the initial paper on LSS in 2002 using the standard distribution method and is what was accepted by the NIH Consensus as clinically meaningful.
- In a separate publication by Inamoto et al, a LSS overall score of 6.1 was presented as clinically meaningful.
- The benchmark of 6-7 on overall LSS is well known in community.
- Determination of the 6-7 benchmark has consistently been based on 0.5 standard deviation of a baseline distribution method (literature).
- Using the benchmark of 7 as context for the descriptive findings of the LSS is reasonable in this study.

The 7 point change is an accepted threshold and is currently accepted benchmark for comparison of this product with other treatments tried to date.

Labeling needs to be relevant for the practitioner and use if possible those tools that are commonly used.

Durability is important. The language in the proposed label will report the LSS symptom bother improvement and provide some information on sustained response.

4) Use of a composite score which does not reflect what the actual patient reported changes occurred

The comment refers to the fact that most of the reported improvements were in the skin and eyes and mouth items. Patients with cGVHD have a very heterogeneous presentation across multiple organs. From Dr. Wroblewski's review she wrote:

There is not one consistent presentation of the signs and symptoms of cGVHD. The LSS encompasses the most commonly affected organs and related cGVHD symptoms and is comprehensive in capturing the relevant symptoms for patients with cGVHD. The LSS has been validated and is widely used in the transplantation community.

The items on the LSS composite index were identified as the core issues that most impacted the patients' lives, an approach that minimizes noise from potential treatment-related toxicities or symptoms that might result more commonly from other unrelated causes.

At baseline, patients enrolled in this study had involvement: skin (81%), mouth (86%), gastrointestinal (33%), lungs (10%), platelet (5%) and liver (17%). So it is not surprising that the majority of the improvement seen in this trial were the organs that were most commonly involved.

5) Limitations due to the term "bother" not describing adequately what is a considered covered by the term "symptom" and additional concerns regarding terminology and what is covered in the subscale.

It should be noted that, by design, the LSS measures symptom bother as distinguished from symptom intensity. The degree to which patients report that they are bothered by a symptom represents a global assessment incorporating not only the intensity of the symptom and its frequency, but also the degree to which it causes emotional disturbance or interferes with functioning.

Because "bother" may better describe what LSS reports and therefore will use the term bother in labeling.

The Division acknowledges that the LSS could be improved and for that reason, the information regarding the LSS results from the trial will be limited.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval

Fulfillment of PMR 2060-3

- Risk Benefit Assessment

cGVHD is a serious complication of hematopoietic stem cell transplant. The first line treatment is corticosteroids. If steroids are not successful in managing the disease, there are no other agents approved to treat the disease. Imbruvica was successful in achieving an improvement in the disease for approximately

2/3 of those enrolled and was durable. Only two new safety issues were identified fall and sepsis.

- Recommendation for Post marketing Risk Management Activities

None other than routine surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

Because cGVHD is complex and the submitted data is from a single arm trial, a PMR will be issued to provide data from a randomized controlled trial. For wording of the PMR, please see the approval letter.

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
08/02/2017