Pharmacyclics LLC

IMBRUVICA® (Ibrutinib, PCI-32765, JNJ-54179060)

Overall Reviewer's Guide

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1. GENERAL INFORMATION

The present Supplemental New Drug Application (sNDA) to NDA No. 205552 concerns ibrutinib (IMBRUVICA, PCI-32765, JNJ 54179060) 140 mg hard gelatin capsules as a single-agent oral therapy to treat patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.
The recommended dose for the treatment of cGVHD is 420 mg (3 x 140 mg capsules) of ibrutinib administered orally, once daily, at approximately the same time each day. The capsules should be swallowed whole with a glass of water.

1.1. Applicant Name and Address

Pharmacyclics LLC (Pharmacyclics)
995 East Arques Ave.
Sunnyvale, CA 94085-4521, USA.

In December 2011, Pharmacyclics entered into a joint development agreement with Janssen Research & Development, LLC (JRD), located at 920 US Highway 202, Raritan, NJ 08869, USA. As part of this agreement, Pharmacyclics delegated conduct of some of the studies included in this application to JRD. JRD also completed some of the documents included herein.

1.2. Application Number

NDA No. 205552

1.3. Trade Name

IMBRUVICA®

1.4. Name of the Active Substance

ibrutinib

2. OVERVIEW

This Overall Reviewer's Guide presents a brief description of the format and content of each module of this sNDA to facilitate locating and understanding each of the documents contained therein. Details of each major module and its respective content are further described below.

This application has been prepared in accordance with the FDA's input.

3. REGULATORY HISTORY

Pharmacyclics received approvals for IMBRUVICA for the following indications;

- Accelerated approval for the treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy on 13 November 2013
- Accelerated approval for the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy on 12 February 2014
- Full approval for the treatment of patients with CLL who have received at least one prior therapy, and approval for the treamtment of patients with CLL with 17p deletion on 28 July 2014
- Full approval for the treatment of patients with Waldenström's Macroglobulinemia (WM) on 29 January 2015
- Full approval for the treatment of patients with CLL on 04 March 2016
- Full approval for the treatment of patients with CLL/SLL, and dosing of IMBRUVICA® (ibrutinib) with bendamustine and rituximab in patients with CLL/SLL; full approval for the treatment of patients with CLL/SLL with 17p deletion on 06 May 2016
- Accelerated approval for the treatment of patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy on 18 January 2017

A list of the key FDA correspondences regarding this application is located in Module 1.6.3 Correspondences Regarding Meetings.

Pharmacyclics was granted the following designations in support of this sNDA submission:

Designation Granted	Indication	Approval Date	Location
Breakthrough Therapy	For the treatment of cGVHD after failure of 1 or more lines of systemic therapy	22 Jun 2016	Module 1.7.1
Orphan Drug	For the treatment of cGVHD	23 Jun 2016	Module 1.2

4. GENERAL FORMAT OF THE SUPPLEMENTAL NDA

The pivotal Phase 1b/2 clinical study PCYC-1129-CA in support of this application for the treatment of patients with cGVHD after failure of one or more lines of systemic therapy is outlined below:

Study No.	Study Title
PCYC-1129-CA	A Multicenter Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependant or Refractory Chronic Graft versus Host Disease

The module 2 summary documents and Study 1129 Clinical Study Report (CSR) do not describe MZL as an approved indication as it has been only recently approved (18 January 2017).

Patent Information

The US patents 7514444; 8008309; 8697711; 8735403; 8754091; 8957079; 9181257 and 9296753 have been submitted previously with an sNDA (SN 0164; MZL Efficacy Supplement) and are currently listed under NDA 205552. These patents continue to claim the drug or method of using the drug for which approval is sought in the current NDA Supplement.

Efficacy narratives

Efficacy narratives for all 42 patients in the all-treated population from pivotal study PCYC-1129-CA are provided in Attachment 5 of the PCYC-1129-CA CSR.

Safety narratives

Safety narratives have been written for the below categories of adverse events and are provided in Attachment 4 to the Study 1129 Clinical Study Report (CSR):

- Subjects who died within 30 days of last dose of study treatment
- Subjects who discontinued study treatment due to an adverse event
- Subjects who experienced a treatment emergent (TE) major hemorrhage event as defined in the protocol
- Subjects who developed a new malignancy (for non-melanoma skin cancer, only serious adverse events have a written narrative)
- Subjects who experienced a TE Serious Adverse Event (SAE) of atrial fibrillation

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