CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig2s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Imbruvica (ibrutinib)

Date: August 21, 2013
To: File for NDA 205552
From: John K. Leighton, PhD, DABT
Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting review for Imbruvica 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 Imbruvica may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/

JOHN K LEIGHTON
08/21/2013

MEMORANDUM

Date: August 20, 2013
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 205552
Drug: IMBRUVICA (ibrutinib) capsules
Indications: treatment of patients with MCL who have received at least one prior therapy and treatment of patients with CLL who have received at least one prior therapy
Applicant: Pharmacyclics, Inc.

Ibrutinib is a small molecule tyrosine kinase inhibitor developed for the treatment of mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). 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.

Transient lymphocytosis reported in patients treated with IMBRUVICA may be due to reduced homing of leukocytes as expected based on the pharmacology studies. GI, skin and musculoskeletal disorders have been reported in patients and are listed in the label. The ongoing studies in patients will provide additional information on the toxicities associated with ibrutinib.

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.

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.

The nonclinical studies needed to support product labeling were reviewed by Drs. Shwu-Luan Lee, Brian Chiu, Margaret Brower, and George Chang. The nonclinical findings are summarized in the "Executive Summary" of the NDA review and reflected in the product label.

Recommendation: I concur with the pharmacology/toxicology reviewers that from a nonclinical perspective, IMBRUVICA may be approved and that no additional nonclinical studies are needed to support approval of IMBRUVICA for the proposed indications.

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