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APPLICATION NUMBER:

209935Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209935
Supporting document/s:	1
Sponsor's letter date:	1/30/2017
CDER stamp date:	1/30/2017
Product:	Kisqali Femara Co-pack
Indication:	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in postmenopausal women
Sponsor:	Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ 07936
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	C.J. George Chang, DVM, MS, PhD, DABT
Supervisor/Team Leader:	Todd Palmby, PhD
Division Director:	John K. Leighton, PhD, DABT (Julia Beaver, MD, Acting)
Project Manager:	Amy Tilley, RPM

1 Executive Summary

1.1 Introduction

Kisqali Femara Co-pack is a co-package of Kisqali (ribociclib) and Femara (letrozole) tablets. Ribociclib is a kinase inhibitor and letrozole is a nonsteroidal aromatase inhibitor.

The Applicant submitted on January 30, 2017 an NDA, which included proposed labeling, for market approval of Kisqali Femara Co-pack. Since this co-pack is a combination product, it required submission of a new NDA, but neither of the individual products are new molecular entities.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical information was provided in support of this Co-pack NDA and nonclinical data for Kisqali and Femara were referenced from the previously reviewed NDAs 209092 and 20726, respectively. Novartis is the Applicant for both referenced NDAs. The majority of the pharmacology/toxicology review of this NDA was focused on the co-pack package insert, which consolidated labeling information of both Kisqali and Femara.

1.3 Recommendations

1.3.1 Approvability

The Pharmacology/Toxicology team recommends approval of NDA for the Kisqali Femara Co-pack.

1.3.2 Additional Non Clinical Recommendations

none

1.3.3 Labeling

The Femara package insert was not previously in PLLR format according to the Pregnancy and Lactation Labeling Rule, so the nonclinical information for letrozole was updated in this co-pack label to be consistent with PLLR. The nonclinical sections containing information for ribociclib were mostly copied from the approved package insert for Kisqali. The majority of changes for letrozole nonclinical information were not substantive and included moving information to the appropriate section and including greater detail when necessary. Refer to the RPM labeling review for specific agreed upon labeling. The following sections contain proposed changes from the pharmacology/toxicology team and the rationale for those changes:

Section 5.4:
Embryo-Fetal Toxicity: “Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI FEMARA CO-PACK and for at least **3 weeks** after the last dose.”

Section 8.3:
Females and Males of Reproductive Potential: Advise females of reproductive potential to use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment with KISQALI FEMARA CO-PACK and for at least **3 weeks** after the last dose.

Section 17:
Embryo-Fetal Toxicity: Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during KISQALI FEMARA CO-PACK therapy and for at least **3 weeks** after the last dose.

Lactation: Advise women not to breastfeed during KISQALI FEMARA CO-PACK treatment and for at least **3 weeks** after the last dose.

Rationale of Acceptance: We typically recommend 5 half-lives or 1 month, whichever is longer, for a drug that causes embryo-fetal toxicity but is not clearly genotoxic, such as ribociclib and letrozole. Since no guidance document is currently publically available to provide this recommendation, we accept the Applicant's proposed duration of **3 weeks**, which accounts for 5 half-lives of letrozole and ribociclib and is consistent with the approved Kisqali label.

2 Drug Information

2.1 Drug

Generic Name	ribociclib
Code Name	LEE001
Pharmacologic Class	kinase inhibitor

Generic Name	letrozole
Code Name	CGS 20267
Pharmacologic Class	aromatase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 209092 (Kisqali); NDA 20726 (Femara)

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/s/

CHING-JEY G CHANG
04/18/2017

TODD R PALMBY
04/21/2017