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APPLICATION NUMBER:

209935Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

REV-CLINPHARM-02 (Review Noted (NAI))

NDA-209935

ORIG-1

Supporting Document 1

New/NDA

Proprietary Name/Request for Review

Form 3674

User Fee/Coversheet

Submit Date: 01/30/2017 - FDA Received Date: 01/30/2017

NDA 209935 cross references to NDA 209092. NDA 209935 and NDA 209092 share identical Clinical Pharmacology package. Refer to Clinical Pharmacology section (section 6) of Multi-disciplinary Review and Evaluation NDA 209092 in DARRTS Dated 03/13/2017 for Clinical Pharmacology review.

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/s/

WENTAO FU
03/30/2017

QI LIU
03/30/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	209935	SDN	1
Applicant	Novartis	Submission Date	1/30/2017
Generic Name	Ribociclib and Letrozole CO-PACK	Brand Name	KISQALI® FEMARA® CO-PACK
Drug Class	KISQALI is a kinase inhibitor; FEMARA is an aromatase inhibitor		
Indication	KISQALI FEMARA CO-PACK is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.		
Dosage Regimen	KISQALI FEMARA CO-PACK tablets should be coadministered orally, once daily, with or without food KISQALI: recommended starting dose is 600 mg orally (3 x 200 mg tablets) for consecutive days followed by 7 days off KISQALI treatment. FEMARA: 2.5 mg (1 tablet) continuously for a 28-day cycle		
Dosage Form	KISQALI Tablets: (b) (4) 200 mg FEMARA Tablets: 2.5 mg	Route of Administration	oral
OCP Division	Division V	OND Division	OHOP/ DOP1
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Wentao Fu, PhD	Qi Liu, PhD	
Pharmacometrics			
Genomics			
Review Classification	☒ Standard ☐ Priority ☐ Expedited		
Filing Date	3/6/2017	74-Day Letter Date	Click here to enter a date.
Review Due Date	TBD	PDUFA Goal Date	Click here to enter a date.

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

- Yes
 No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

- Yes
 No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

- Yes
 No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies Yes No Clinical Pharmacology Summary Yes No
 Bioanalytical and Analytical Methods Yes No Labeling Yes No

Comments: NDA 209935 cross references to NDA 209092. Tabular Listing of All Human Studies, Clinical Pharmacology Summary and Bioanalytical and Analytical Methods are included in NDA 209092 submission

Clinical Pharmacology Studies

Comments: There is no Clinical Pharmacology study in this submission. Refer to NDA209092 Clinical Pharmacology Filing Review (Darrts Date 10/04/2016) for Clinical Pharmacology Studies cross referenced by this submission.

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☐ Bioequivalence		
☐ Food Effect		
☐ Other		
Human Pharmacokinetics		
Healthy Subjects	☐ Single Dose	
	☐ Multiple Dose	
Patients	☐ Single Dose	
	☐ Multiple Dose	
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☒ Patients		
Pharmacokinetics/Pharmacodynamics		

☐ Healthy Subjects				
☐ Patients				
☐ QT				
Pharmacometrics				
☐ Population Pharmacokinetics				
☐ Exposure-Efficacy				
☐ Exposure-Safety				
Total Number of Studies		In Vitro		In Vivo
Total Number of Studies to be Reviewed				

Criteria for Refusal to File (RTF)

Comments: Refer to NDA209092 Clinical Pharmacology Filing Review

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐ Yes ☐ No ☐ N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐ Yes ☐ No ☐ N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐ Yes ☐ No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐ Yes ☐ No ☐ N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐ Yes ☐ No ☐ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐ Yes ☐ No ☐ N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐ Yes ☐ No ☐ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☐ Yes ☐ No ☐ N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☐ Yes ☐ No ☐ N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	☐ Yes ☐ No ☐ N/A	

previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Comments: Refer to NDA209092 Clinical Pharmacology Filing Review		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐ Yes ☐ No ☐ N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐ Yes ☐ No ☐ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐ Yes ☐ No ☐ N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐ Yes ☐ No ☐ N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐ Yes ☐ No ☐ N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐ Yes ☐ No ☐ N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐ Yes ☐ No ☐ N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☐ Yes ☐ No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐ Yes ☐ No ☐ N/A	

Filing Memo

There is no Clinical Pharmacology study result in this submission. All the clinical pharmacology study results are cross referenced to NDA 209092. In NDA 209092, the same dosing regimen for KISQALI and FEMARA were proposed for the same indication by the same applicant. This NDA 209935 submission proposed CO-PACK of KISQALI and FEMARA. The study results in NDA 209092 submission are used to support the approval of KISQALI and FEMARA CO-PACK.

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