CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209935Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209935
Review #1

Drug Name/Dosage Form	Kisqali Femara Co-Pack ribociclib and letrozole Tablets
Strength	200 mg (ribociclib); 2.5 mg (letrozole)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 0000	1/30/2017	Drug product
Labeling/PI 0001	2/28/2017	Drug product
Labeling/CC 0002	3/6/2017	Drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Paresma Patel	CDER/OPQ/ONDP/DNDP1
Process	Paresma Patel	CDER/OPQ/ONDP/DNDP1
Microbiology	N/A	CDER/OPQ/ONDP/DNDP1
Facility	Marion Michaelis	CDER/OPQ/OPF/DIA
Biopharmaceutics	Gerlie Gieser	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	Paresma Patel	CDER/OPQ/ONDP/DNDP1

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	Type II	N/A				
	Type III *(if applicable)*	N/A				
	Type IV *(if applicable)*	N/A				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	209092	Kisqali® (ribociclib) tablets
NDA	020726 S-031	Femara (letrozole) tablets
IND	(b) (4)	
IND	117796	Breast cancer for ribociclib

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

CMC information for Kisqali® Femara Co-Pack tablets is provided by referencing the respective NDA 209092 for Kisqali® (Ribociclib) tables and NDA 020726 for Femara (letrozole) tables. Both NDAs are approved and current, and the referenced drug products are legally manufactured in the US. The facility review recommends "Approval" for all manufacturing facilities involved in both NDAs. Therefore, the NDA is recommended for **Approval** from the CMC standpoint.

A Post Marketing Approval Commitment (PMC) has been proposed and agreed on by the applicant that is provided below:

- Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations.
- Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031), and if MVTR/tablet data of the proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration.
- Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottle of Femara.

Final Report Submission: 10/2017

II. Summary of Quality Assessments

A. Product Overview

The NDA was submitted to seek approval for the co-packaged (200 mg) ribociclib and (2.5 mg) letrozole tablets. Letrozole is US marketed drug since its approval by FDA in 1997. Ribociclib, in combination with letrozole, was recently approved (2017) under NDA 209092 for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. The ribociclib plus letrozole "co-pack" is to facilitate both patient compliance and convenience, simplifying adherence to the 28-day cycle dosing regimen and allowing an easier distribution option to patients.

Proposed Indication(s) including Intended Patient Population	KISQALI FEMARA CO-PACK [ribociclib, a kinase inhibitor, in combination with letrozole, an aromatase inhibitor] 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.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	• KISQALI: recommended starting dose is 600 mg orally (3 (b) (4) 200 mg tablets) for 21 consecutive days followed by 7 days off KISQALI treatment. • (b) (4) • FEMARA: 2.5 mg (1 tablet) continuously for a 28-day cycle
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Product Background: Kisqali Femara Co-Pack is copackaged Kisqali 200 mg immediate release tablets and Femara 2.5 mg tablets. Kisqali was approved 10-Mar-2017 under NDA 209092 and Femara was approved on 25-July-1997 under NDA 020726.

Drug Product Name / Strength: KISQALI Femara CO-PACK; Ribociclib (Kisqali) film-coated tablets, 200 mg; Letrozole (Femara) film-coated tablets, 2.5 mg

Route of Administration: Oral Administration

The proposed drug product is a co-package of two drug products, Kisqali (ribociclib) 200 mg film-coated tablets and Femara (letrozole) 2.5 mg film-coated tablets. The co-pack is developed for a 28 day cycle for dosing of ribociclib (21 tablets and 1 week off) and letrozole (28 tablets). There are no changes to the manufacturing of these two individual drugs that will be included in the co-pack. CMC information for ribociclib is cross referenced to NDA 209092. CMC information for letrozole is cross referenced to NDA 020726. The supplement S-031 for NDA 020726 provides for a comparability protocol of the study to compare Moisture Vapor Transition Rate per tablet (MVTR/tablet) (USP <671>) of the proposed 28-tablet count presentation of letrozole to the marketed 30-tablet count presentation, both of which are packaged into the 90-cc HDPE bottles of the same construction and materials. If the MVRT/tablet of the proposed 28-count presentation falls within the MVTR/tablet range for approved packaging counts, Novartis expects the new container count for co-packaging Femara w/Ribociclib Film coated tablet to be stable over the currently approved Femara shelf life. NDA 020726/S031 was reviewed by Dr. Lorenzo Rocca, and found the proposed comparability acceptable (review filed in

Panorama on 05-Apr-2017). The S031 supplement was approved on 7-Apr-2017. The data for the comparability study will be submitted as a CBE supplement to NDA 20726.

Since the data for the comparability protocol has not been generated, a PMC was initiated by the FDA and agreed by the applicant as described below:

- *Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations.*
- *Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031), and if MVTR/tablet data of the proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration.*
- *Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottle of Femara.*

Final Report Submission: *10/2017*

All facility information for both drug products was submitted in their respective NDAs except one facility submitted in the drug product section of this application for secondary packaging of the co-pack, (b) (4) This facility happens to do primary packaging of Femara as well. Based on the evaluation for this additional activity the recommendation is "Approval".

The applicant requests a categorical exclusion from the requirement for preparation of an Environmental Assessment. It is found acceptable since the amount of ribociclib in the co-pack is within the estimated usage for the approved NDA 209092. The amount of letrozole in the co-pack is not expected to increase beyond what has been approved in NDA 209092.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A.

D. Final Risk Assessment (see Attachment)

Refer to NDA 209092.

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D. ***April 30, 2017***

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LABELING

R Regional Information

1.14 Labeling

The most recent container labels for Kisqali Femara Co-pack were submitted on 27-Mar-2017 (SD4) and outer carton labels on 24-Apr-2017 (SD7). The carton and container labels are copied and reviewed below. The applicant revised the carton and container labels based on recommendations from DMEPA. Refer to the review by Tingting Gao submitted in DARRTS on 17-Mar-2017. Minor typographical errors were corrected in the submission dated 24-Apr-2017 (SD7) for the outer carton of the Kisqali Femara Co-pack. The primary packaging labels for the Kisqali blisters and Femara bottles are provided in this submission. Samples of the Kisqali Femara Co-pack were submitted to the Agency.

Kisqali Femara Co-pack is available in three presentations that contain individual ribociclib and letrozole drug products.

1) Kisqali blister packs with 21 tablets per blister pack (7 doses of 3 tablets for each 600 mg dose), and 3 blisters per outer container. One 28-tablet count bottle of Femara 2.5 mg tablets.

2) Kisqali blister packs with 14 tablets per pack (7 doses of 2 tablets for each 400 mg dose), and 3 blisters per outer container. One 28-tablet count bottle of Femara 2.5 mg tablets.

3) Kisqali blister pack with 21 tablets per blister pack (21 doses of 1 tablet for each 200 mg dose), and 1 blister per outer container. One 28-tablet count bottle of Femara 2.5 mg tablets.

Immediate Container Label-Kisqali
Blister Cards-Kisqali:

(b) (4)

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Immediate Container Label-Femara 2.5 mg tablets

(b) (4)

Reviewer's Assessment: ***Adequate.***

Kisqali Blister Card
The blister cards are identical to those approved under NDA 209092 except that different NDC numbers are assigned for the co-pack blisters. Additionally, the statement "(b) (4)" was removed from the 200 mg blister card because the dosing calendars are provided separately. The blister cards meet all regulatory requirements for the immediate container labeling.

Kisqali Blister Sleeve
The blister sleeves differ from the sleeves approved under NDA 209092 in the following:

-"NOT FOR INDIVIDUAL SALE" statement added
-NDC numbers and bar codes are different for the co-packs
- (b) (4) and is enclosed separately to include dosing of Kisqali with Femara

The blister sleeves meet all the regulatory requirements for the immediate container labeling.

Labeling for the Physician samples of the 600 mg dose presentation of Kisqali is provided in the submission and include the statement "Physician Sample – Not For Sale" on the blister card and blister sleeve.

Femara Immediate Labeling
The immediate labels for Femara tablets are consistent with the marketed tablets, except that the co-pack contains 28 tablets per bottle instead of 30 tablets per bottle. Additionally, the 28 tablet Femara bottles include the statement "Not for Individual Sale." All other information is identical. The immediate labeling for Femara bottles meets all regulatory requirements for an oral drug.

Physician samples are also provided in the submission.

Outer Carton Labeling

(b) (4)

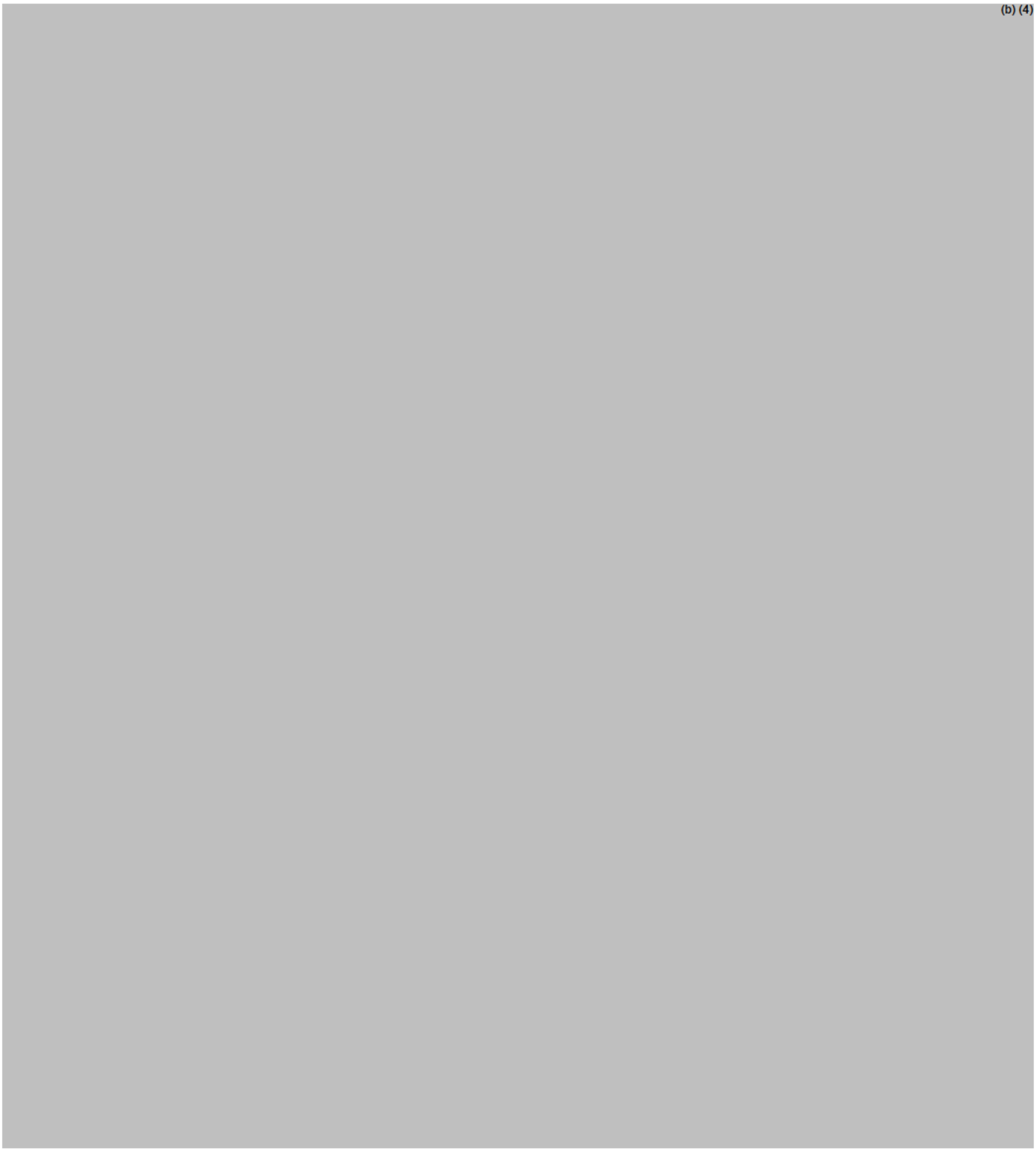


Table 1. *Carton Label Review of Regulatory Requirements*

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		N/A oral drugs
Sterility Information (if applicable)		N/A oral drugs
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2)(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)	The applicant provides dosage nformation on carton and sleeve.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		N/A oral drugs

Reviewer's Assessment: *Adequate.*
The applicant revised the outer carton labeling during the review cycle based on recommendations from DMEPA. Refer to the review by Tingting Gao submitted in DARRTS on 17-Mar-2017. The presentation of the proprietary name was changed from [redacted] to 'Kisqali Femara CO-PACK' based on DMEPA recommendations. The applicant further updated the outer carton labeling on 24-Apr-2017 to correct minor typographical errors.

The revised outer carton labels submitted on 24-Apr-2017 (SD 7) meet all regulatory requirements as shown above in Table 1.

Package Insert

The package insert was revised in response to suggestions from the review team. The revised PI was submitted on 24-Apr-2017. The suggested modifications to the PI from DMEPA and CMC are shown in the assessment section, and the applicant's response is evaluated.

Highlights

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets:

- KISQALI : 200 mg (3)
- FEMARA: 2.5 mg (3)

Reviewer's Assessment: *Adequate.*
No edits are suggested, the Highlights section Dosage forms and strengths is adequate.

3 DOSAGE FORMS AND STRENGTHS

KISQALI FEMARA CO-PACK [redacted] ribociclib tablets co-packaged with letrozole tablets.

- [redacted] tablet: 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate). Film coated, light greyish violet, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side.
- [redacted] 2.5 mg tablets: dark yellow, film-coated, round, slightly biconvex, with beveled edges (imprinted with the letters FV on one side and CG on the other side).

Reviewer's Assessment: *Adequate.*
The suggested edits include consistency for description of the tablets and are shown in red below.

3 DOSAGE FORMS AND STRENGTHS
KISQALI FEMARA CO-PACK is KISQALI (ribociclib) tablets copackaged with FEMARA (letrozole) tablets.
•Tablets 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate): Film coated, light greyish violet, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side.
•Tablets 2.5 mg letrozole: Dark yellow, film-coated, round, slightly biconvex, with beveled edges (imprinted with the letters FV on one side and CG on the other side).

The applicant made the suggested edits to the Dosage Forms and Strengths section of the PI, and the revised PI was submitted on 24-Apr-2017 (SD 7).

11 DESCRIPTION

KISQALI FEMARA CO-PACK consists of ribociclib 200 mg film coated tablets copackaged with letrozole 2.5 mg tablets.

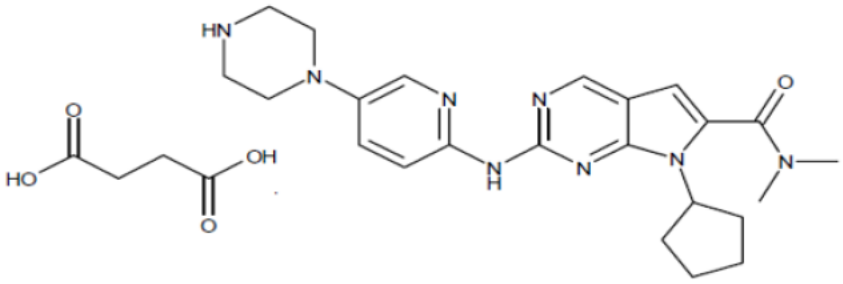
Ribociclib:

KISQALI (ribociclib) is a kinase inhibitor.

The chemical name of ribociclib succinate is: Butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1).

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The molecular formula for ribociclib succinate is $C_{23}H_{30}N_8O.C_4H_6O_4$ and the molecular weight is 552.64 g/mole [*Free base: 434.55 g/mol].*

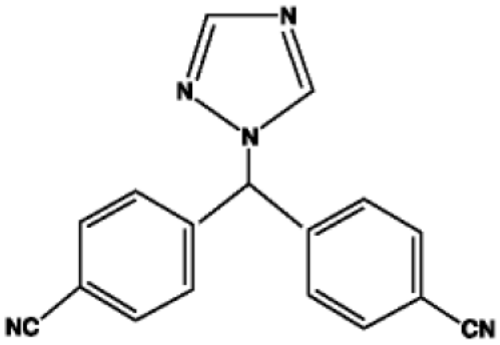
The chemical structure of ribociclib is shown below:



KISQALI film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

Letrozole:

FEMARA [redacted] (b) (4) a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). [redacted] (b) (4) 4,4'-(1H-1,2,4-Triazol-1ylmethylene)dibenzonitrile, and its structural formula is



Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, $C_{17}H_{11}N_5$ empirical formula, and a melting range of 184°C to 185°C.

FEMARA is available as 2.5 mg tablets for oral administration.

Inactive Ingredients: Colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

Reviewer's Assessment: *Adequate.*
The following suggested edits were sent to the applicant: the physical description of ribociclib was added and the empirical formula of letrozole was added. The applicant made additional edits to the letrozole description to be consistent with the ribociclib presentation of information. The edits from the applicant are acceptable.

11 DESCRIPTION

KISQALI FEMARA CO-PACK consists of ribociclib 200 mg film coated tablets copackaged with letrozole 2.5 mg tablets.

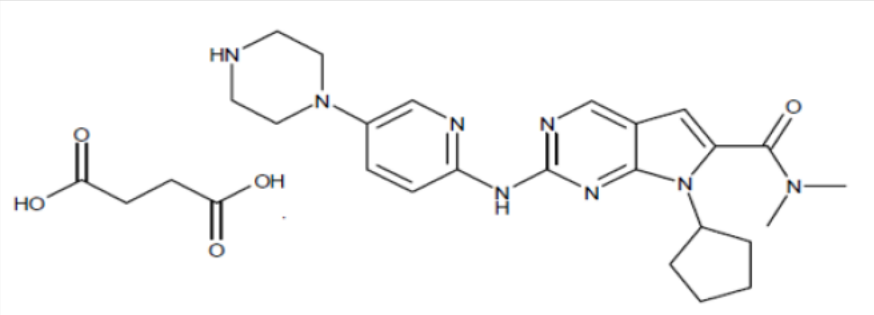
Ribociclib:

KISQALI (ribociclib) is a kinase inhibitor.

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The chemical name of ribociclib succinate is: Butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1).

The molecular formula for ribociclib succinate is $C_{23}H_{30}N_8O.C_4H_6O_4$ and the molecular weight is 552.64 g/mole [*Free base: 434.55 g/mol].*

The chemical structure of ribociclib is shown below:

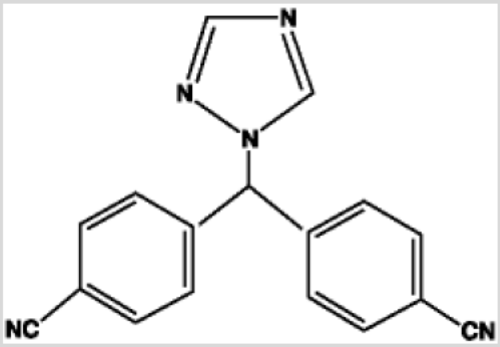


KISQALI film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolyzed ~~hydrolysed~~), talc, titanium dioxide, and xanthan gum as inactive ingredients.

Letrozole:
FEMARA (letrozole) is a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis).

Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31, empirical formula $C_{17}H_{11}N_5$, and a melting range of 184°C to 185°C.

The chemical name of letrozole is 4,4'-(1H-1,2,4-Triazol-1ylmethylene)dibenzonitrile, and its structural formula is



FEMARA is available as 2.5 mg tablets for oral administration.

Inactive Ingredients: Colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

The applicant made the suggested edits to the Description Section of the PI, and the revised PI was submitted on 24-Apr-2017 (SD 7).

16 HOW SUPPLIED/STORAGE AND HANDLING

Store KISQALI FEMARA CO-PACK at 20ºC to 25°C (68ºF to 77°F). Store in the original package.

KISQALI FEMARA CO-PACK is dispensed in a carton for a total of 28 days of therapy.

Each carton contains individual ribociclib and letrozole drug products as follows:

KISQALI (ribociclib) Tablets:

(b) (4) 200 mg (b) (4).

Light greyish violet, round, curved with beveled edge, debossed with "RIC" on one side and "NVR" on the other side.

FEMARA (letrozole) Tablets:

2.5 mg tablets.

Dark yellow, round, slightly biconvex, with beveled edges, imprinted with the letters "FV" on one side and "CG" on the other side.

(b) (4)

KISQALI FEMARA CO-PACK Cartons:

- NDC 0078-XXXX-XX- 3 Blister packs, containing 21 tablets (200 mg per tablet) (600 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

- NDC 0078-XXXX-XX - 3 Blister packs, containing 14 tablets (200 mg per tablet) (400 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

- NDC 0078-XXXX-XX - 1 Blister pack, containing 21 tablets (200 mg per tablet) (200 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

Reviewer's Assessment: *Adequate.*

The following suggested edits were sent to the applicant: the storage information was moved to the end of the section. The description of the tablets for Kisqali was edited to be consistent with Femara. The applicant included the NDC numbers upon submitting the revisions, and submitted an additional correction to the NDC numbers on 24-Apr-2017.

16 HOW SUPPLIED/STORAGE AND HANDLING

KISQALI FEMARA CO-PACK is dispensed in a carton for a total of 28 days of therapy.
Each carton contains individual ribociclib and letrozole drug products as follows:

KISQALI (ribociclib) Tablets:
200 mg tablets.
Light greyish violet, round, curved with beveled edge, debossed with "RIC" on one side and "NVR" on the other side.

FEMARA (letrozole) Tablets:
2.5 mg tablets.
Dark yellow, round, slightly biconvex, with beveled edges, imprinted with the letters "FV" on one side and "CG" on the other side.

KISQALI FEMARA CO-PACK Cartons:

- NDC 0078-0923-61 - 3 Blister packs, containing 21 tablets (200 mg per tablet) (600 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

- NDC 0078- 0916-61 - 3 Blister packs, containing 14 tablets (200 mg per tablet) (400 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

- NDC 0078-0909-61 - 1 Blister pack, containing 21 tablets (200 mg per tablet) (200 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

Store KISQALI FEMARA CO-PACK at 20°C to 25°C (68°F to 77°F). Store in the original package.

The applicant made the suggested edits to How Supplied/Storage and Handling section of the PI, and the final revised PI was submitted on 24-Apr-2017 (SD 7).

Primary Labeling Reviewer Name and Date:

Paresma Patel, Ph.D.
April 24, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D.
April 24, 2017

Paresma Patel

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Anamitro Banerjee

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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: NDA 209935	**Established/Proper Name: ribociclib and letrozole**
Applicant: Novartis Pharmaceuticals	**Dosage Form: tablet; tablets; co-packaged**
Submission Type:505b1	**Strength(s): tablets 200mg; 2.5mg co-packaged**
Chemical Type: small-molecule	**Cross Referenced Applications: ND 117796, (b) (4)** **NDA 209092, NDA 020726**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Describe potential review issues here or on additional sheets

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

The NDA is submitted under 505(b)1 for KISQALI FEMARA CO-PACK, ribociclib and letrozole copackaged. The proposed indication is ribociclib in combination with Letrozole 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. The indication is the same as that of NDA 209,092 (ribociclib), submitted on August 29, 2016 (PDUFA goal date of April 29, 2017). Approval of NDA 209,092 is recommended by the Quality review team. Refer to the IQA dated March 1, 2017 filed in Panorama. Letrozole is an FDA approved drug. A PAS supplement (NDA 020726_S31) for the changing of package configuration (from 30 to 28 counts) to be copackaged with ribociclib tablets was submitted and currently under review. The PDUFA date for this supplement is 21-Apr-2017. CMC information for ribociclib is mostly referenced to NDA 209,092.

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	X			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?			X	
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	X			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	X			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	X			One Facility on pg 9 of 356H Novartis Pharma Stein AG (Drug substance Letrozole manufacturing (b) (4). Manufacture, In-process control testing and release testing of drug product Femara 2.5 mg FCT) Is not chaecked as being ready for inspection. I don't see this as an issue since they do not need an inspection. Their current status is compliant for this profile class of manufacturing.
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	BIOPHARMACEUTICS				

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?			X	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*)	X			The Applicant proposes secondary packaging (using a cardboard box) for the two approved drug products. The cover letter of the current NDA states: "no Clinical, CMC, or Pharmacology/Toxicology data in this NDA…" Refer to the Biopharm Reviews of the original submissions for KISQALI NDA 209,092, and Femara NDA 20-726. Note that S-031 (in house) provides for the Femara® tablet count change [from 30 to 28] consistent with what is required for co-packaging with a 21-day on + a 7 day off regimen of KISQALI. *****NOTE:** **From the Biopharmaceutics perspective, there are no filing or approvability issues. This Filing Review closes out the Biopharmaceutics Review Task for NDA 209935.**
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.		X		
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?		X		
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			X	

C. FILING CONSIDERATIONS					
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?			X	
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			X	
17.	For Biotech Products, is sufficient information provided in compoliance with 21 CFR 610.9 and 601.2(a)?			X	

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	

Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: **This process will be reviewed approximately 150 days from date issued (May 24, 2016).**

Version	**Summary of Changes**	**Date Issued**
01	Initial	05/24/2016

Xiao Chen

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