Clinical Policy Title:	ribociclib, ribociclib-letrozole
Policy Number:	RxA.181
Drug(s) Applied:	Kisqali®, Kisqali® Femara® Co-Pack
Original Policy Date:	02/07/2020
Last Review Date:	04/18/2022
Line of Business Policy Applies to:	All lines of business

Background

Ribociclib (Kisqali®) is a kinase inhibitor indicated for the treatment adult patients with hormone receptor (HR) (HR)-positive, human epidermal growth factor receptor 2 (HER2)- negative advanced or metastatic cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

Ribociclib-letrozole(Kisqali® Femora® Co-Pack), a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated as initial endocrine-based therapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ribociclib (Kisqali®)	Breast cancer	600 mg orally once daily for 21 consecutive days followed by 7 days off treatment	600 mg/day
		Hepatic Impairment Dosing: Moderate to severe hepatic impairment (Child-Pugh class B or C): Reduce the starting dose to 400 mg orally once daily.	
		Renal Impairment Dosing: Severe renal impairment (CrCL less than 30 mL/min): recommended starting dose is 200 mg orally once daily	
ribociclib/letrozole (Kisqali® Femara® Co-Pack)	Breast cancer	600 mg ribociclib orally once daily for 21 consecutive days followed by 7 days off treatment 2.5 mg letrozole orally once a day for a 28-	ribociclib: 600 mg/day

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		day cycle	letrozole: 2.5 mg/day
		Hepatic Impairment Dosing Moderate hepatic impairment (Child-Pugh class B): Reduce the starting dose to 400 mg orally once daily. No dosage adjustment of letrozole is necessary. Severe hepatic impairment (Child-Pugh class C): Reduce the starting dose of ribociclib to 400 mg orally once daily. If the patient has cirrhosis, reduce the dose of letrozole to 2.5 mg by mouth every other day; the effect of hepatic impairment on letrozole exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.	
		Renal Impairment Dosing Severe renal impairment (CrCL less than 30 mL/min): The recommended starting dose is 200 mg orally once daily. No dosage adjustment of letrozole is required for patients with CrCL 10 mL/min or higher.	

*If the dose of ribociclib is reduced to less than 200 mg/day, therapy should be discontinued.

Dosage Forms

- Ribociclib (Kisqali®): Tablets: 200 mg
- Ribociclib/letrozole (Kisqali® Femara® Co-Pack): Tablets: 200 mg ribociclib, 2.5 mg letrozole

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**

1. Diagnosis of recurrent unresectable or stage IV breast cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age 18 years of age or older;
4. Disease has all of the following characteristics (a, b, and c):
   a. HR-positive (i.e., estrogen receptor (ER) and/or progesterone receptor (PR) positive);
   b. HER2-negative;
   c. Advanced (locally recurrent) or metastatic;
5. If request is for ribociclib, therapy is prescribed in combination with one of the following (a or b):

a. An aromatase inhibitor (e.g., letrozole, anastrozole, exemestane);
b. Fulvestrant;

6. If male and receiving an aromatase inhibitor, therapy is prescribed in combination with an agent that suppresses testicular steroidogenesis (e.g., gonadotropin-releasing hormone agonists such as Lupron, Trelstar, Zoladex);
7. Request meets one of the following (a or b):*
   a. Dose does not exceed ribociclib 600 mg per day (3 tablets per day for 21 days) and letrozole 2.5 mg per day (1 tablet per day for 28-day cycle);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval Duration
Commercial: 12 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Breast Cancer (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is currently receiving ribociclib or ribociclib-letrozole for breast cancer and has received this medication for at least 21 days;
3. Member is responding positively to therapy;
4. Dose of ribociclib is at least 200 mg per day;
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed ribociclib 600 mg per day (3 tablets per day for 21 days) and letrozole 2.5 mg per day (1 tablet per day for 28-day cycle);
   b. New dose is supported by practice guideline or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CDK: Cyclin-Dependent Kinase
ER: Estrogen Receptor
FDA: Food and Drug Administration
HER2: Human Epidermal Growth Factor Receptor 2
HR: Hormone Receptor
NCCN: National Comprehensive Cancer Network
PR: Progesterone Receptor

APPENDIX B: Therapeutic Alternatives
Not Applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Kisqali®: None reported.
  - Kisqali® Femara® Co-Pack: Known hypersensitivity to letrozole or any of its excipients.

*Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- For disease progression while on a CDK4/6 inhibitor, there is no data to support retreatment with another CDK4/6 inhibitor-containing regimen.
- Although the NCCN currently supports the use of Kisqali® with tamoxifen (category 1; breast cancer guidelines v1.2018), a warning was recently added to Kisqali®'s prescribing information noting concerns for increased QT prolongation observed with concomitant use in the MONALEESA-7 trial.

References

1. Kisqali® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2021. Available at: https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf Accessed January 5, 2022.
2. Kisqali® Femara® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=aa5e4446-19cd-4235-a382-5b48bf6c3b2f&type=display Accessed January 5, 2022.
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5. Ribociclib. Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 05, 2022.
6. Ribociclib/letrozole. Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 05, 2022.
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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	03/2020	02/07/2020
Policy updated. 1. Formatting updated. 2. Clinical title updated. 3. Continued criteria for approval updated. 4. Approval duration updated. 5. Reference updated.	07/28/2020	09/14/2020
Policy was reviewed: 1. Clinical policy section standard verbiage was updated to include "The provision of prescriber samples…".	03/31/2021	06/10/2021

2. Continued therapy approval criteria II.A.1 was updated to “Member is currently receiving medication…”. 3. References were updated.		
Policy was reviewed: 1. Background: Updated indication from Ribociclib, in combination with an aromatase inhibitor, and ribociclib-letrozole are indicated as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer to Ribociclib Ribociclib (Kisqali®) is a kinase inhibitor indicated for the treatment adult patients with hormone receptor (HR) (HR)-positive, human epidermal growth factor receptor 2 (HER2)- negative advanced or metastatic cancer in combination with: • an aromatase inhibitor as initial endocrine-based therapy; or • Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men. 2. Dosing Information, Dosing Regimen, ribociclib (Kisqali®): Updated to include hepatic impairment & renal impairment dosing information for indication Breast cancer. 3. Dosing Information, Dosing Regimen ribociclib/letrozole (Kisqali® Femara® Co-Pack): Updated to include hepatic impairment & renal impairment dosing information for indication Breast cancer. 4. Initial Approval Criteria, I.A.1 Updated indication from Diagnosis of recurrent or stage IV breast cancer to Diagnosis of recurrent unresectable or stage IV breast cancer. 5. Initial Approval Criteria I.A.6 updated to remove off label. 6. Initial Approval Criteria I.A.5.c was updated to remove Tamoxifen (off-label), and medical justification supports need to use tamoxifen over an aromatase inhibitor or fulvestrant. 7. Appendix C, Contraindications: Updated to include new contraindication Known hypersensitivity to letrozole or any of its	01/05/2022	04/18/2022

excipients. 8. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 9. References were reviewed and updated.		