abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO050

Description

Abemaciclib (Verzenio), palbociclib (Ibrance) and ribociclib (Kisqali) are orally administered cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, which suppress the activity of CDK 4/6 enzymes in tumor cells leading to inactivation of certain tumor suppressor genes

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
abemaciclib (Verzenio)	50 mg tablets	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (women)	56 tablets/28 days
	100 mg tablets		
	150 mg tablets		
	200 mg tablets		
palbociclib (Ibrance)	75 mg capsules/tablets*	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (men and women)	21 capsules or tablets/28 days
	100 mg capsules/tablets*		
	125 mg capsules/tablets*		
ribociclib (Kisqali)	200 mg tablet dose pack	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (women)	21 tablets/28 days
	400 mg tablet dose pack		42 tablets/28 days
	600 mg tablet dose pack		63 tablets/28 days
ribociclib/letrozole (Kisqali/Femara)	200 mg and 2.5 mg tablet dose pack		49 tablets/28 days
	400 and 2.5 mg tablet dose pack		70 tablets/28 days
	600 and 2.5 mg tablet dose pack		91 tablets/28 days

Initial Evaluation

I. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication will not be used in combination with any other oncolytic medication, with the exception of an aromatase inhibitors (e.g. anastrozole, letrozole) or estrogen receptor antagonist (e.g. fulvestrant); **AND**
   D. Member has <u>not</u> previously progressed on, or after, treatment with another CDK4/6 inhibitor (e.g. ribociclib [Kisqali], abemaciclib [Verzenio]); **AND**
   E. Diagnosis of **breast cancer** when the following are met:
      1. The Member has hormone receptor-positive (HR+) and HER2-negative (HER2-) disease; **AND**
      2. Disease is advanced (stage III) or metastatic (stage IV); **AND**
      3. Request is for treatment as first line chemotherapy in combination with an aromatase inhibitor (e.g. letrozole, anastrozole, exemestane); **AND**
         i. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g. GnRH therapy [e.g. Lupron] used concomitantly]); **OR**
         ii. The member is male; **AND**
            a. The request is for palbociclib (Ibrance); **AND**
            b. Palbociclib (Ibrance) will be administered in combination with a GnRH analog (e.g. goserelin, leuprolide); **OR**
      4. Request is for treatment as second line or subsequent-line chemotherapy; **AND**
         i. The member has progressed after first line endocrine therapy (e.g. aromatase inhibitor, or estrogen receptor modulator [e.g. tamoxifen]); **AND**
            a. The medication will be administered in combination with fulvestrant (Faslodex); **AND**
            b. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g. GnRH therapy [e.g. Lupron] used concomitantly]); **OR**
            c. The member is male; **AND**
               i. The request is for palbociclib (Ibrance); **OR**
         ii. The member has previously progressed following endocrine therapy and chemotherapy; **AND**
            a. The member's current disease stage is metastatic (stage IV); **AND**
            b. The member is female; **AND**

c. Member received endocrine therapy and chemotherapy (not containing a CDK 4/6 inhibitor) in the metastatic (stage IV) setting; **AND**
d. The request is for abemaciclib (Verzenio) monotherapy

II. Abemaciclib (Verzenio), palbociclib (Ibrance) and ribociclib (Kisqali) are considered investigational when used for all other conditions, including but not limited to:
   A. In combination with, or following progression on or after, another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio])
   B. For the treatment of breast cancer in males (ribociclib [Kisqali], abemaciclib [Verzenio] only)
   C. Pancreatic neuroendocrine tumors (pNET)
   D. Ovarian or endometrial cancer
   E. Central nervous system cancers (e.g., glioma, astrocytoma, head and neck, etc.)
   F. Colorectal cancer
   G. Urothelial or renal cell carcinoma
   H. Leukemias and lymphomas
   I. Non-small-cell lung cancer
   J. Liposarcoma
   K. Biliary tract carcinoma
   L. Head and neck cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
III. The medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. The medication will **not** be used in combination with any other oncolytic medication with the exception of an aromatase inhibitor (e.g., anastrozole, letrozole) or fulvestrant (Faslodex); **AND**
V. Member has exhibited improvement or stability of disease symptoms (e.g. decrease in tumor size, or tumor spread)

Supporting Evidence

I. Abemaciclib (Verzenio), palbociclib (Ibrance,) and ribociclib (Kisqali) were not studied in patients under 18 years of age; therefore, their efficacy and safety in the pediatric population is unknown.

II. Many treatment options exist for advanced and metastatic breast cancer. Initial and subsequent therapies in this setting are contingent upon patient specific characteristics. Given the complexities surrounding the diagnosis and treatment options, targeted drug therapies such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors should be prescribed by, or in consultation with, an oncologist.

III. Abemaciclib (Verzenio) was evaluated in adult, female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were pivotal trials for the approved indications:

- MONARCH 3: Verzenio in Combination with an Aromatase Inhibitor. The trial evaluated postmenopausal women with no prior systemic therapy, and was a randomized, double-blinded, placebo-controlled trial. Premenopausal women were administered GnRH therapy for at least two weeks prior to initiation of therapy for ovarian suppression and continued throughout the trial. The primary efficacy outcome was Progression-Free Survival (PFS), which favored abemaciclib (Verzenio). A secondary outcome was objective response rate (ORR), which also favored abemaciclib (Verzenio); however, overall survival (OS) data is not yet available.
- MONARCH 2: Verzenio in Combination with Fulvestrant. The trial evaluated subjects with disease progression on or after adjuvant metastatic endocrine therapy, and was a randomized, placebo-controlled trial. The primary and secondary outcomes mirror that of MONARCH 3, in favor of abemaciclib (Verzenio); however, OS data was not mature at time of FDA-approval.
    i. The OS data from this trial was reported in September 2019. There was statistically significant OS in favor of abemaciclib (Verzenio) in combination with fulvestrant versus placebo by 9.4 months.
- MONARCH 1: Verzenio Administered as a Monotherapy in Metastatic Breast Cancer. The trial, a single-arm, open-label trial, evaluated women who received prior endocrine therapy and one-to-two lines of chemotherapy in the metastatic setting. The primary outcomes were ORR and median duration of response (DOR).

IV. Initial FDA-approval of palbociclib (Ibrance) was for women only and was evaluated in adults with breast cancer with the following characteristics: HR+, HER2-, advanced (stage III) or metastatic (stage IV) disease. There were two settings evaluated: initial endocrine based therapy in combination with an aromatase inhibitor and treatment in combination with fulvestrant after progression on initial endocrine therapy.

V. Palbociclib (Ibrance) was further FDA-approved for breast cancer in men in 2019. The approval was based on data from electronic health records and post marketing reports of real-world use

in male patients. The sources of data included the following: IQVIA Insurance database, Flatiron Health Breast Cancer database, and the Pfizer global safety database. Guidelines recommend that men on an aromatase inhibitor and palbociclib (Ibrance) be administered a GnRH analog concurrently. Available evidence suggests that those treated with aromatase inhibitor monotherapy have been associated with inferior outcomes; likely due to inadequate estradiol suppression.

VI. Ribociclib (Kisqali) was evaluated in adult, female subjects with HR-positive, HER2-negative, advanced or metastatic breast cancer. Please note, ribociclib (Kisqali) has NOT been evaluated in males.

- MONALEESA-2: Randomized, double-blind, placebo-controlled trial comparing ribociclib (Kisqali) in combination with letrozole versus placebo with letrozole. Subjects were treatment naïve for their disease. The outcomes were progression-free survival (PFS) and overall response rate (ORR), which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole.
- MONALEESA-7: Kisqali in Combination with an Aromatase Inhibitor. Randomized, double-blind, placebo-controlled trial of pre-perimenopausal subjects evaluating ribociclib (Kisqali) plus an aromatase inhibitor or tamoxifen with goserelin versus an aromatase inhibitor or tamoxifen and goserelin. Concomitant therapy with GnRH agonist (goserelin) was utilized in order to induce menopause in all participants. The outcomes included PFS and ORR, which were statistically significant in favor of ribociclib (Kisqali).
    i. Overall survival data was reported in June 2019 and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).
- MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for treatment of postmenopausal women who had received zero to one line of prior endocrine therapy. This was compared to placebo plus fulvestrant. Efficacy primary outcomes were PFS and ORR which were statistically significant in favor of ribociclib (Kisqali).
    i. Overall survival data was reported in September 2019 (HR: 0.74 [p=0.00455]) in favor of ribociclib (Kisqali).

VII. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence, in combination with therapies outside of aromatase inhibitors and fulvestrant, remain unknown. The National Comprehensive Cancer Network (NCCN) notes a lack of data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen. As of September 2020, NCCN guidelines stated “If there is disease progression while on a CDK4/6 inhibitor, there is no data to support an additional line of therapy with another CDK4/6 inhibitor-containing regimen. Of note, those that are unable to tolerate other CDK4/6 inhibitors

and are switching to palbociclib (Ibrance) prior to progression would be acceptable candidates for therapy."

VIII. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, exemestane. Chemotherapy regimen include, but may not be limited to, the following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

IX. There is lack of scientific evidence from randomized controlled trials supporting the safety and/or efficacy for increased dosing or frequency of palbociclib (Ibrance). The dosing recommendation is one capsule once daily, with various doses for tolerability and dose adjustments for safety considerations, in 21 out of 28-day cycles. Increasing the dose beyond 125 mg per day, or dosing more than 21 out of every 28 days has not been evaluated.

X. Postmenopausal status may be reached in women via ovarian suppression through GnRH therapy (pharmacotherapy-induced) for several weeks prior to palbociclib (Ibrance) administration, bilateral oophorectomy (surgically-induced), ovarian irradiation, or natural menopause. Any of these routes is considered acceptable for aforementioned criteria.

XI. The NCCN Guidelines do not currently distinguish a preference between currently available CDK4/6 inhibitors (abemaciclib, palbociclib ribociclib) and no evidence is currently available indicating that one of these agents is superior than the other. A prospective analysis of the efficacy data of abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) as first- or second-line therapies in ER-positive advanced breast cancer noted that these agents had similar efficacy. To date, no large head to head comparison is currently available to support or oppose this conclusion.

Investigational or Not Medically Necessary Uses

I. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence in combination with therapies outside of aromatase inhibitors and fulvestrant remain unknown. National Comprehensive Cancer Network (NCCN) notes a lack of data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen. As of September 2020, NCCN guidelines stated "If there is disease progression while on a CDK4/6 inhibitor, there is no data to support an additional line of therapy with another CDK4/6 inhibitor-containing regimen. Of note, those that are unable to tolerate other CDK4/6 inhibitors and are switching to palbociclib (Ibrance) prior to progression would be acceptable candidates for therapy.

II. There is currently no evidence supporting the use of CDK4/6 inhibitors for other types of cancer, other than the indications listed in this policy.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of wording related to GnRH therapy to induce menopause in order to clarify the FDA approval for Kisqali in pre/perimenopausal setting	03/2021
Merged all CDK 4/6 inhibitor policies into one policy.	12/2020
Previews reviews • Verzenio: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice and removal of subgroup analysis exclusions, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); added new indication: first-line treatment in combination with an aromatase inhibitor (2018); clarified use of concomitant medication (2017) • Kisqali: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice (2019); updated product availability with Kisqali-Femara dose pack, added new indication for pre/perimenopausal setting in combination with aromatase inhibitor, as well as postmenopausal setting in combination with fulvestrant as first or second line endocrine therapy, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2018) • Ibrance: Updated QL box to inform about transition to tablets (2020), Added new indication and FDA-approval of breast cancer in men, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); updated criteria to allow treatment after disease progression on prior endocrine therapy (2016)	03/2020 10/2019 05/2019 09/2018 08/2018 03/2018 09/2017 01/2016
Criteria created • Verzenio • Kisqali • Ibrance	10/2019 04/2017 02/2015