Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors
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 (CDK 4/6) inhibitors, which suppress the activity of CDK 4/6 enzymes in tumor cells leading to the inactivation of certain tumor suppressor genes.

Length of Authorization
- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
abemaciclib (Verzenio)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic; early-stage breast cancer	50 mg tablets	56 tablets/28 days
		100 mg tablets	
		150 mg tablets	
		200 mg tablets	
palbociclib (Ibrance)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	75 mg capsules/tablets	21 capsules or tablets/28 days
		100 mg capsules/tablets	
		125 mg capsules/tablets	
ribociclib (Kisqali)	Early-stage breast cancer	200 mg tablet dose pack	21 tablets/28 days
		400 mg tablet dose pack	42 tablets/28 days
	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	200 mg tablet dose pack	21 tablets/28 days
		400 mg tablet dose pack	42 tablets/28 days
		600 mg tablet dose pack	63 tablets/28 days

Initial Evaluation

I. **Abemaciclib (Verzenio), palbociclib (Ibrance), or 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. Member has <u>not</u> previously progressed on, or after, treatment with another cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor[e.g., ribociclib (Kisqali), abemaciclib (Verzenio), palbociclib (Ibrance)]; **AND**
   D. Member has a diagnosis of hormone receptor-positive (HR+) and human epidermal growth factor-negative (HER2-) breast cancer; **AND**
   E. The request is for **adjuvant therapy of early-stage (stage II-III) breast cancer (EBC)**; **AND**

1. The member has undergone definitive surgical resection of the primary tumor; **AND**
2. The member has received or completed therapy using one of the following treatment modalities:
    i. Endocrine-based therapy (e.g., fulvestrant, tamoxifen, letrozole, anastrozole, exemestane, etc.); **OR**
    ii. Radiotherapy; **OR**
    iii. Taxane (e.g., docetaxel, paclitaxel) and/or anthracycline (e.g., doxorubicin) based chemotherapy; **AND**
3. The request is for abemaciclib (Verzenio); **AND**
    i. Abemaciclib (Verzenio) will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or tamoxifen; **AND**
    ii. Treatment will not be used in combination with any additional oncology therapy; **AND**
    iii. Provider attests the member has high-risk breast cancer based on one the following:
        a. Histopathological tests showing four or more (≥ 4) axillary lymph nodes are affected (pALN N2 or N3 disease); **OR**
        b. Histopathological tests showing one to three axillary lymph nodes are affected (N1 disease), and one of the following:
            i. Tumor size is ≥ 5 cm; **OR**
            ii. Histopathological grade 3 disease (G3); **OR**
            iii. The member has a Ki-67 score ≥ 20% as determined by an FDA-approved test; **OR**
4. The request is for ribociclib (Kisqali); **AND**
    i. Ribociclib (Kisqali) will be used in combination with an aromatase inhibitor (letrozole, anastrozole, exemestane); **OR**
    ii. Treatment will not be used in combination with any additional oncology therapy; **AND**
    iii. Provider attests the member is at high risk of recurrence; **AND**
    iv. Member has node-positive disease (N1, N2, N3); **OR**
    v. Member has no regional lymph node involvement [i.e., node-negative disease (N0)]; **AND**
        a. Tumor size ≥ 5 cm (T3-T4); **OR**
        b. Tumor size 2 – 5 cm (T2); **AND**
            i. Histopathological grade 3 disease (G3); **OR**
                1. Histopathological grade 2 disease (G2); **AND**
                    a. Member is determined to be high risk via gene expression assay (e.g., Oncotype DX

Breast Recurrence Score ≥ 26; genomic profiling assays (i.e., Prosigna/PAM50, MammaPrint, or EndoPredict EPclin), etc.) or Ki-67 score ≥ 20%; **OR**

F. The request is for **advanced (stage III) or metastatic breast cancer (stage IV)**; **AND**
   1. The medication is prescribed as a first line therapy; **AND**
      i. Treatment will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or fulvestrant (Faslodex); **AND**
      ii. The member is postmenopausal or receiving hormone suppression (e.g., surgical ablation, suppression with gonadotropin-releasing hormone (GnRH) therapy [e.g., leuprolide], etc.); **AND**
      iii. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali); **AND**
         a. Medication will not be used in combination with any additional oncology therapy; **OR**
      iv. The request is for palbociclib (Ibrance); **AND**
         a. Medication will not be used in combination with any additional oncology therapy; **AND**
            i. Documentation that treatment with abemaciclib (Verzenio)* or ribociclib (Kisqali)* is contraindicated or not tolerated; **OR**
         b. The request is for palbociclib (Ibrance) in combination with inavolisib (Itovebi)* and fulvestrant (Faslodex); **AND**
            i. Documentation of *PIK3CA* mutation; **AND**
            ii. Member has not previously progressed on a *PIK3CA* active agent (e.g., alpelisib [Piqray], capivasertib [Truqap]); **AND**
            iii. Breast cancer is endocrine resistant, defined by disease progression on, or within, 12 months of completing adjuvant therapy (e.g., letrozole, anastrozole, exemestane, tamoxifen); **AND**
            iv. Medication will not be used in combination with any other oncology therapy except for fulvestrant (Faslodex) and inavolisib (Itovebi)*; **OR**
   2. The medication is prescribed as second line therapy; **AND**
      i. Treatment will be used in combination with fulvestrant (Faslodex); **AND**
      ii. Will not be used in combination with any additional oncology therapy; **AND**
      iii. The member had disease progression on, or after primary endocrine therapy (as adjuvant or first-line systemic therapy); **AND**

iv. The member is postmenopausal or receiving hormone suppression (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **AND**
    a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali); **OR**
    b. The request is for palbociclib (Ibrance); **AND**
        i. Documentation that treatment with abemaciclib (Verzenio)* or ribociclib (Kisqali)* is contraindicated or not tolerated; **OR**

3. The medication is prescribed as third line or later therapy in the metastatic (stage IV, M1) setting; **AND**
    i. Member had disease progression on, or after, endocrine therapy and systemic chemotherapy (not containing a cyclin-dependent kinase 4/6 [CDK 4/6] inhibitor) in the metastatic (stage IV) setting; **AND**
    ii. The request is for abemaciclib (Verzenio) monotherapy

**Please note: medications notated with an asterisk may require additional review.*

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 cyclin-dependent kinase 4/6 (CDK 4/6 inhibitor) (e.g., ribociclib [Kisqali], abemaciclib [Verzenio], palbociclib [Ibrance])
    B. Ribociclib (Kisqali) or abemaciclib (Verzenio) in combination with inavolisib (Itovebi)
    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 through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. 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 estrogen receptor antagonist (e.g., tamoxifen, fulvestrant (Faslodex) or palbociclib (Ibrance) in combination with inavolisib (Itovebi)* and fulvestrant (Faslodex); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., decrease in tumor size, or tumor spread)

Please note: medications notated with an asterisk may require additional review.

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 (CDK 4/6) inhibitors should be prescribed by, or in consultation with, an oncologist.
III. **Abemaciclib (Verzenio):** Abemaciclib (Verzenio) was evaluated as an early-stage adjuvant therapy, first-line or subsequent-line systemic chemotherapy in adult, female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were pivotal trials for the approved indications:
    a. MONARCH-E: Abemaciclib (Verzenio) was studied in the setting of adjuvant therapy for early-stage breast cancer with high risk of recurrence or metastasis, in an open-label, randomized, phase 3 trial (MONARCH-E) in 5,637 patients. Efficacy and safety of adding abemaciclib (Verzenio) to endocrine therapy (aromatase inhibitor or tamoxifen) was compared with conventional endocrine therapy. Abemaciclib (Verzenio) was administered for 2 years following a definitive tumor reduction surgery and chemotherapy with taxane and/or anthracycline in adjuvant or neoadjuvant setting. High risk was defined based on the following key factors: ≥ 4 pALN disease; or 1 to 3 positive ALN in the setting of a tumor of at least 5 cm or larger, or histologic grade 3 disease. A Ki-67 index ≥ 20% in untreated breast tissue as determined by an FDA approved test was required as a marker for high-risk of recurrence (Ki-67 is a cancer antigen protein and serves as a marker for tumor cell mitosis). Invasive disease-free survival (IDFS) was the primary endpoint. A pre-specified analysis reflecting a median follow-up of 4.5 years was published October 2023. All patients have completed the abemaciclib (Verzenio)

treatment course, with more than 80% of patients having been followed for at least two years after completion. In the intent-to-treat (ITT) population, the risk of developing invasive disease was reduced by 32% (HR=0.680, 95% CI (0.599- 0.772); p<0.001). The absolute increase in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) continued to deepen in magnitude at five years, to 7.6% and 6.7%, respectively, reflecting improvements from the two-, three-, and four-year rates. With the majority of the IDFS events being DRFS events, the DRFS benefit was also maintained with abemaciclib (Verzenio) reducing the risk of developing distant recurrence or death by 32.5% (HR=0.675, 95% CI (0.588 - 0.774); p<0.001). While overall survival (OS) data remain immature, fewer deaths were observed in the abemaciclib (Verzenio) arm (208 [7.4%] of 2,808 patients) compared to the control arm (234 [8.3%] of 2,829 patients) (HR=0.903, 95% CI (0.749- 1.088); p = 0.284). Nearly twice as many patients receiving ET alone (n=269) developed and are living with metastatic disease compared to those receiving Verzenio (n=138).

   i. As of March 2023, the FDA removed the Ki-67 testing requirement for adjuvant abemaciclib as the benefit of adjuvant use was demonstrated regardless of Ki-67 status, which allows more patients with high-risk, HR+, HER2-negative early breast cancer to be eligible for treatment.

b. MONARCH 3: Abemaciclib (Verzenio) in combination with an aromatase inhibitor. The trial evaluated postmenopausal women and 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). The final OS analysis (at data cut off September 2023) resulted in longer OS in abemaciclib (Verzenio) compared to aromatase inhibitor however statistical significance was not reached. The observed improvement in median OS was 13.1 months (66.8 for abemaciclib + aromatase inhibitor vs. 53.7 placebo + aromatase inhibitor (HR 0.804 (95%CI 0.637 – 1.015; p=0.0664)).

c. MONARCH 2: Abemaciclib (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. At the final interim data cut-off reported in 2020, the ITT population (n=446) analysis reported median OS of 46.7 months for abemaciclib (Verzenio) plus fulvestrant and 37.3 months for placebo plus fulvestrant (HR= 0.757; 95% CI, 0.606-0.945; P = 0.01). Improvement in OS was consistent across all stratification

factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR 0.675; 95%CI, 0.511-0.891) and primary resistance to prior ET (HR 0.686; 95%CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months) was also statistically significantly improved.

ii. MONARCH 1: Abemaciclib (Verzenio) administered as a monotherapy in metastatic breast cancer. The trial, a single-arm, open-label, phase II 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). Abemaciclib (Verzenio) induced partial response in 19.7% and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5). Median PFS was 6 months (95% CI: 4.2–7.5). At the final analysis, at 18 months, median OS was 22.3 months (95% CI: 17.7–not reached).

iii. postMONARCH: Designed to show the benefit of continued treatment with CDK4/6 inhibitor therapy for patients (N=182) with HR+/HER2− advanced breast cancer that progressed or recurred after previous CDK4/6 inhibitor therapy. In postMONARCH, 182 patients were treated with (abemaciclib) Verzenio plus fulvestrant, and 186 patients were treated with placebo plus fulvestrant. The primary endpoint was investigator-assessed PFS; key secondary endpoints included PFS by blinded independent central review (BICR), OS, and ORR. Results from the primary analysis of postMONARCH with 258 events were presented at ASCO 2024. PFS rates at 6 months were 50% in the Verzenio-plus-fulvestrant arm and 37% in the placebo-plus-fulvestrant arm (HR, 0.73, 95% CI, 0.57–0.95). BICR-assessed PFS rates at 6 months were 68% in the Verzenio-plus-fulvestrant arm and 45% in the placebo plus-fulvestrant arm (HR, 0.55; 95% CI, 0.39–0.77). The investigator-assessed ORR was 17% in the Verzenio-plus-fulvestrant arm and 7% in the placebo-plus fulvestrant arm, and the BICR-assessed ORRs were 23% and 8%, respectively. Prespecified subgroup analysis showed a PFS benefit favoring Verzenio plus fulvestrant:

1. Patients on a prior CDK4/6 inhibitor for <12 months: HR, 0.80; 95% CI, 0.50–1.29.
2. Patients on a prior CDK4/6 inhibitor for ≥12 months: HR, 0.70; 95% CI, 0.52–0.94.
3. A consistent effect was seen across major clinical and genomic subgroups, including patients with baseline ESR1 or PIK3CA mutations.

IV. **Palbociclib (Ibrance):** Palbociclib (Ibrance) was evaluated as a first-line or subsequent-line systemic chemotherapy in adult male and female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were trials have evaluated the safety and efficacy of palbociclib (Ibrance) for the approved indications:

a. PALLAS: Prospective, randomized, phase III trial evaluated patients with HR+/HER- early breast cancer were randomly assigned to receive 2 years of palbociclib (Ibrance) with adjuvant endocrine therapy or adjuvant endocrine therapy alone (for at least 5 years). The primary end point of the study was iDFS. The study concluded the addition of adjuvant palbociclib (Ibrance) to standard endocrine therapy did not improve outcomes over endocrine therapy alone in patients with early HR+/HER2- eBC. At a median follow-up of 31 months, IDFS events occurred 8.8% patients who received palbociclib (Ibrance) plus endocrine therapy vs. 9.1% patients who received endocrine therapy alone, with similar results between the two treatment groups (iDFS at 4 years: 84.2% v 84.5%; HR= 0.96; 95% CI 0.81 to 1.14, p=0.65).
b. PALOMA-2: Palbociclib (Ibrance) plus aromatase inhibitor (letrozole) vs. placebo and letrozole in postmenopausal women receiving first-line treatment for HR+/HER2- mBC. This was a Phase III, randomized, double-blind, trial where subjects had no prior treatment in the metastatic setting. The results showed that palbociclib (Ibrance) plus letrozole resulted in an improved median PFS of 24.8 months compared to letrozole+placebo at 14.5 months (HR =0.58; 95% CI, 0.46 to 0.72; p <0.0001). The final OS analysis published June 2022 reported no significant survival benefit with palbociclib (Ibrance) plus letrozole over letrozole and placebo. After a median follow-up of 90 months, patients receiving palbociclib (Ibrance) + letrozole had numerically longer OS compared to letrozole monotherapy (median 53.9 months vs median 51.2 months), however the results were not statistically significant (HR=0.96; 95% CI: 0.78-1.18; *P*=0.3378).
c. PALOMA-3: Palbociclib (Ibrance) and fulvestrant vs. fulvestrant in pre- or post-menopausal HR+, HER2- advanced breast cancer patients, whose disease progressed on prior endocrine therapy in the adjuvant or metastatic setting. The median PFS was 9.5 months for the combination compared to 4.6 months for fulvestrant (HR= 0.46; 95% CI: 0.36 to 0.59; p< 0.0001). Key secondary endpoints were ORR and OS. ORR was achieved by 24.6% patients on palbociclib (Ibrance) + fulvestrant vs 10.9% on fulvestrant. An OS difference of 6.9 months was seen; median OS was 34.9 months with palbociclib (Ibrance) + fulvestrant vs 28.0 months with fulvestrant (HR=0.81; 95% CI: 0.64-1.03; p=0.09). At the updated non-prespecified OS analysis with a data cut off August 2020, data showed a numerical difference in median OS in favor of palbociclib (Ibrance), but did not reach statistical significance.
d. PENELOPE-B: Palbociclib (Ibrance) for 1 year was examined as adjuvant therapy in the metastatic setting in women who still had residual disease after undergoing neoadjuvant chemotherapy versus placebo. The study did not meet the primary endpoint of improved IDFS in women with HR+/HER- eBC.
e. P-REALITY X: Real-world effectiveness of 1L use of palbociclib (Ibrance) + letrozole vs letrozole monotherapy in HR+/HER2- mBC. This was an observational, retrospective

analysis of electronic health records (EHRs) of 2888 postmenopausal women and men. The primary endpoint was OS. After stabilized inverse probability treatment weighting, median OS was 49.1 months among palbociclib (Ibrance) vs. 43.2 months vs letrozole (HR=0.76; 95% CI, 0.65-0.87; p<0.0001). Progression-free survival was 19.3 months vs versus 13.9 months, respectively (HR= 0.70; 95% CI, 0.62-0.78; p<0.0001).

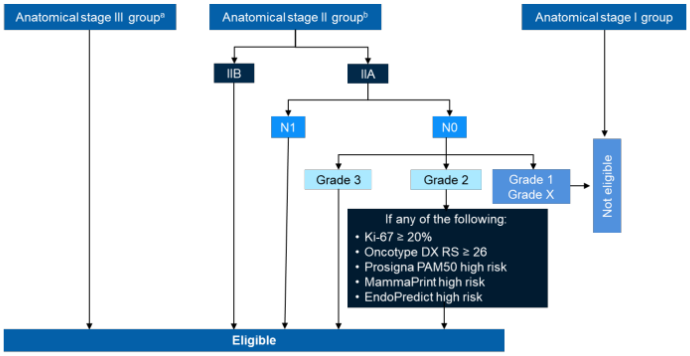
f. INAVO120: A Phase 3, double-blind, placebo-controlled trial (n=325) studying patients with HR+/HER2-, PIK3CA mutated, endocrine resistant, locally advanced or metastatic breast cancer with progression during, or within, 12 months of completing adjuvant endocrine treatment with an aromatase inhibitor or tamoxifen, and in combination with inavolisib (Itovebi) and fulvestrant. Patients who had progressed with CDK 4/6 inhibitors in the neoadjuvant or adjuvant setting more than 12 months after finishing CDK 4/6 inhibitor therapy were included in the study (n=4). Patients receiving prior systemic therapy for metastatic breast cancer and those with HbA_{1C} >6% or diabetes were excluded. The majority of participants were female (98%), White (59%), with three or more organs with metastases (51%), secondary endocrine resistance (66%), and neoadjuvant or adjuvant chemotherapy (83%) and tamoxifen (48%) use. The primary efficacy outcome was median progression free survival (PFS) which was statistically significant and in favor of inavolisib (Itovebi), palbociclib (Ibrance), and fulvestrant (Faslodex) treatment arm (15 months) compared to placebo, palbociclib (Ibrance), and fulvestrant (Faslodex) (7.3 months), HR 0.43 (0.32-0.59), p<0.001. Median overall survival was immature at the time of data cut-off. The overall quality of the data is low due to lack of mature OS data and use of surrogate outcomes (e.g., PFS) which do not have a strong correlation with improvements in OS in metastatic breast cancer space.

V. **Ribociclib (Kisqali):** Ribociclib (Kisqali) was evaluated in adults with HR-positive, HER2-negative, early, advanced, and metastatic breast cancer.

a. NATALEE: Randomized phase III, open label clinical trial comparing ribociclib (Kisqali) + nonsteroidal aromatase inhibitor (AI) as adjuvant treatment in patients with HR+/HER2- early breast cancer compared to AI alone. Patients (N=5,101) were randomized 1:1 to receive ribociclib (Kisqali) 400mg per day for 21 days on and 7 days off for 3 years along with an AI (letrozole or anastrozole) for >5 years plus goserelin in males and premenopausal females. NATALEE utilized a lower starting dose (400mg) of ribociclib than the metastatic breast cancer starting dose of 600mg to improve tolerability while maintaining efficacy. The study included patients with stage II or III disease with either lymph node–positive or –negative disease, which is a contrast to [abemaciclib] monarchE trial, which only enrolled patients with lymph node-positive disease. The primary endpoint was investigator-assessed invasive disease–free survival (iDFS) and secondary end points included recurrence-free survival (RFS), distant disease-free survival (DDFS), overall survival (OS), and safety and tolerability. At the time of the prespecified interim analysis, the median follow-up was 44.2 months, the iDFS rate was 90.8% with ribociclib

(Kisqali) plus an AI vs 88.1% with an AI alone (HR = 0.715; 95% CI (0.609–0.840), P =0.0001). Findings from subgroup analyses revealed that patients with stage II (HR=0.644; 95% CI, 0.468-0.887) and stage III (HR=0.737; 95% CI, 0.611-0.888) disease experienced an iDFS benefit with the addition of ribociclib (Kisqali) to AI. An iDFS benefit was also observed with the addition of ribociclib in patients with N0 (HR= 0.666; 95% CI, 0.397-1.118) and N1 to N3 (HR=0.731; 95% CI, 0.617-0.866) nodal status. At a median follow-up for OS of 44.3 months, the addition of ribociclib to an AI led to a reduction in the risk of death vs AI therapy alone (HR=0.827; 95% CI, 0.636-1.074; *P* = 0.0766) [follow-up for OS is still ongoing]. The 3-year regimen of ribociclib (Kisqali) at a 400-mg starting dose plus an AI was not associated with any new safety signals. Any-grade adverse effects of special interest occurring in the intervention and control arms included neutropenia (63% vs 5%), liver-related AEs (27% vs 11%), and interstitial lung disease/pneumonitis (2% vs 1%). Other clinically relevant any-grade AEs included arthralgia (39% vs 44%), nausea (24% vs 8%), headache (23% vs 17%), and fatigue (23% vs 14%).

i. As of November 2024, the NCCN guidelines for early breast cancer list ribociclib and abemaciclib as preferred category 1 recommendations for adjuvant treatment in HR+, HER2- early breast cancer at a high risk of recurrence. The NCCN further breaks down high risk of recurrence for ribociclib that mirrors the population of the NATALEE trial: patients with any lymph node involvement or if no nodal involvement either tumor size >5 cm, or if tumor size 2-5 cm, either Grade 2 (and high genomic risk or Ki-67 ≥20%), or Grade 3.
ii. While the use of these assays is not required for staging, gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. The NCCN guidelines recommend the following gene expression assays for conversation of adjuvant systemic treatment: Oncotype DX Breast Recurrence Score $\underline{\geq}$ 26, Prosigna/PAM50, MammaPrint, or EndoPredict EPclin. The guidelines also recommend testing for Ki-67 if HR+, HER2- and considering a adjuvant CKD4/6 inhibitor.
iii. Figure 1. NATALEE Enrollment (source supplementary appendix Slamon D, Lipatov O, Nowecki Z, et al 2024)



AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or supraclavicular lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm but less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.

[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3).

[b] Capped at 40% (≈ 2000 patients). Simplified inclusion criteria are used in the illustration.

iv.

b. MONALEESA-2: Randomized, double-blind, placebo-controlled trial comparing ribociclib (Kisqali) in combination with letrozole versus placebo with letrozole in 1L postmenopausal patients with HR/HER2- mBC. Subjects were treatment naïve for their disease. The outcomes were PFS and ORR, which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole. Median OS data was published March 2022, showed OS 64 months with ribociclib (Kisqali) plus letrozole and 51 months with placebo plus letrozole (HR =0.76; 95% CI, 0.63 to 0.93; P = 0.008).
c. MONALEESA-7: Ribociclib (Kisqali) in combination with an aromatase inhibitor in 1L premenopausal patients. 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. The outcomes included PFS and ORR, which were statistically significant in favor of ribociclib (Kisqali). Overall survival data was reported in June 2019 and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).
d. MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for 1L/2L 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). At 42 months, estimated survival rates among patients who received first-line therapy were 66.9% with ribociclib (Kisqali) plus fulvestrant versus 56.3% with fulvestrant alone. The median OS among patients in the early-relapse and second-line subgroup was 40.2 months with ribociclib (Kisqali) plus fulvestrant and 32.5 months with fulvestrant alone.

e. MAINTAIN: Randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus CKD4/6i in patients with unresectable or metastatic HR+/HER2 breast cancer. The trial enrolled 120 postmenopausal women, but GnRH agonist was allow if premenopausal and/or men and less than one line of chemotherapy for metastatic breast cancer. The trial assessed PFS as the primary endpoint and ORR as a secondary endpoint. At 30 months, PFS was 5.3 vs. 2.8 for ribociclib + ET and placebo + ET, respectively (HR 0.57 (95% CI 0.39 – 0.95), p=0.006)).

VI. **Treatment of breast cancer in men:** few men have been included in breast cancer clinical trials. As such natural incidence of breast cancer in men is rare (<1%), which has also reflected in the clinical trials' sample population. Therefore, recommendations regarding management of breast cancer in men are generally extrapolated from the findings of clinical trials in women.

a. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) have received FDA-approval in the setting of treatment of breast cancer in men. For abemaciclib (Verzenio) and ribociclib (Kisqali), this indication also extends in the adjuvant setting for the treatment of early breast cancer with high risk of recurrence.

b. Palbociclib (Ibrance) was 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. NCCN Guidelines recommend that men on an aromatase inhibitor and palbociclib (Ibrance) be administered a GnRH analog concurrently.

c. In the preoperative/adjuvant therapy setting, chemotherapy with or without HER2-targetted therapy is recommended in the male population. Typical adjuvant endocrine therapy options for men with breast cancer include tamoxifen, or if tamoxifen is contraindicated, an aromatase inhibitor in combination with a GnRH analog. In men, single-agent adjuvant treatment with an aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen monotherapy, likely due to inadequate estradiol suppression.

d. Similarly, when aromatase inhibitor is used in combination with a CDK 4/6 inhibitor for the treatment of advanced or metastatic breast cancer in men, additional therapy with a GnRH analog (e.g., leuprolide) is recommended by NCCN guidelines for breast cancer. However, few retrospective studies involving treatment of men with metastatic breast cancer using aromatase inhibitors with or without GnRH analog showed that concurrent use of GnRH analog or type of aromatase inhibitor used did not provide statistically significant advantage in outcomes- progression free survival (PFS), and overall survival (OS).

VII. In early HR+, HER2- breast cancer, adjuvant CDK 4/6 inhibitors have been studied in high-risk patients who mostly received adjuvant/neoadjuvant chemotherapy and there are limited data in

those who did not receive chemotherapy. The NATALEE trial evaluating ribociclib (Kisqali) allowed endocrine-based therapy for up to 12 months prior to randomization, being the most inclusive endocrine-based therapy eligibility window of any CDK4/6 inhibitor trial in eBC. Therefore, patients that began endocrine therapy within the last year may still be candidates for treatment with ribociclib (Kisqali). The monarchE for abemaciclib (Verzenio) allowed endocrine-based therapy for ≤12 weeks prior to randomization. In patients with germline BRCA1/2 mutation eligible for adjuvant olaparib, abemaciclib, or ribociclib, the optimal sequence of therapy and benefit is not known. In the adjuvant setting, abemaciclib (Verzenio) duration of therapy is two years, compared to three years for ribociclib (Kisqali). In absence of head-to-head trials, it is unclear whether longer CDK 4/6 inhibitor treatment in EBC may improve long-term survival and safety profiles, and patient adherence will need to be monitored in clinical practice.

VIII. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK 4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD 4/6 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 NCCN notes a lack of data to support use of an additional CDK 4/6 inhibitors after progression on a CDK 4/6 regimen. As of November 2024, the NCCN guidelines note “If there is disease progression while on palbociclib, there are limited phase II data to support the use of ribociclib in the second line setting.” However, the optimal sequencing of CDK 4/6 inhibitors is still unknown. Benefits of continuing CDK 4/6 inhibitor beyond progression remain controversial and largely unknown at this time, necessitating high quality randomized controlled trials to explore this question. PostMONARCH, a Phase 3 study, and MAINTAIN, a Phase 2 study, evaluated this question, demonstrating improved progression free survival (PFS) when abemaciclib (Verzenio) or ribociclib (Kisqali) was used after progression on CDK 4/6 inhibitors; however, overall survival data remains immature, precluding any conclusions of the impact on overall survival. The PALMIRA trial looked at continuing palbociclib (Ibrance) in the second line setting after previous progression on a palbociclib (Ibrance) based regimen. Results demonstrated that continuing palbociclib (Ibrance) did not significantly improve PFS compared to second-line endocrine therapy alone. ELAINE 3 and EMBER 3 are other trials evaluating this question, results of which are not available at this time. Currently, there is no high-quality prospective data to suggest that continuation of CDK 4/6 inhibitor beyond initial progression is effective and more high-quality data is required before this approach can be considered standard.

IX. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, and exemestane. Of note, the NCCN guidelines state “VTE risk should be considered when combining abemaciclib with tamoxifen.” Chemotherapy regimens include, but may not be limited to, the following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

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 the aforementioned criteria.

XI. As of November 2024, the NCCN guidelines do not currently distinguish a preference between currently available CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) and no evidence is currently available indicating that one of these agents is superior to 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 (e.g. anastrozole) and estrogen receptor antagonists (e.g. tamoxifen, fulvestrant) remain unknown. National Comprehensive Cancer Network (NCCN) acknowledges there are limited data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen.

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.

III. Abemaciclib (Verzenio) and ribociclib (Kisqali) received FDA approval in the setting of adjuvant therapy of high-risk early-stage breast cancer (EBC). Palbociclib (Ibrance) failed to show iDFS benefit in patients with HR+/HER2–negative early breast cancer vs. adjuvant endocrine therapy in the PALLAS and PENELOPE-B trials, therefore treatment with palbociclib in EBC is considered not medically necessary.

Appendix

I. The tumor, node, metastasis (TNM) TNM system is the most common method of cancer staging in breast cancer. Numbers or letters after T, N, and M give more details about each characteristic. Higher numbers mean the cancer is more advanced.
   a. T refers to the size and extent of the main (primary) tumor.
      i. Tis: non-invasive cancer found only in ducts (carcinoma in situ)
      ii. TX: Main tumor cannot be measured
      iii. T0: Main tumor cannot be found
      iv. T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into

nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.

b. The N refers to the number of nearby lymph nodes involved that have cancer
    i. NX: Cancer in nearby lymph nodes cannot be measured (e.g., previously removed, etc.)
    ii. N0: There is no cancer in nearby lymph nodes
    iii. N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer
c. The M refers to whether the cancer has metastasized
    i. MX: Metastasis cannot be measured
    ii. M0: Cancer has not spread to other parts of the body
    iii. M1: Cancer has spread to other parts of the body (distant metastasis)

II. Breast cancer is often staged before and after surgery. Clinical staging (c) is referred to staging before treatment (cTNM) and pathologic stage (p) is based on the results of tissue samples removed during surgery (pTNM).

III. Tumor grade is dependent on tumor histology. A low-grade tumor has a lower risk of recurrence. A high-grade tumor tend to grow/spread faster and have a higher risk for recurrence.
a. GX: Grade cannot be determined
b. G1: Low grade
c. G2: Intermediate grade
d. G3: High grade

IV. As of September 2024, ribociclib (Kisqali) package insert notes it should now be refrigerated before dispensing but can be stored at room temperature for up to 2 months by patients.
a. Ribociclib (Kisqali) in advanced or metastatic breast cancer is given as 600 mg (3 x 200-mg tablets) orally, once daily (3 weeks on, 1 week off) with either an aromatase inhibitor once daily (continuously); in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines; or Fulvestrant 500 mg intramuscularly on Days 1, 15, and 29, and once monthly thereafter; in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines.
b. In eBC, the adjuvant dosing studied was ribociclib 400-mg for 3 years.
c. If dose reduction below 200 mg/day is required, discontinue treatment

V. Abemaciclib (Verzenio) dosing
a. Recommended starting dose in combination with fulvestrant, tamoxifen, or an aromatase inhibitor: 150 mg twice daily.
b. Recommended starting dose as monotherapy: 200 mg twice daily.

c. In eBC, the adjuvant dosing studied was abemaciclib 150-mg for 2 years or until disease recurrence or unacceptable toxicity
d. Dosing interruption and/or dose reductions by 50mg may be required based on individual safety and tolerability. Discontinue ribociclib for patients unable to tolerate 50 mg twice daily.

VI. 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.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
olaparib (Lynparza)	Early, high-risk breast cancer
everolimus (Afinitor)	Advanced breast cancer
talazoparib (Talzenna)	Locally advanced or metastatic breast cancer
Gonadotropin-releasing hormone (GnRH)	Advanced prostate cancer
	Advanced breast cancer in premenopausal women
alpelisib (Piqray, Vijoice)	Breast cancer, HR+, HER2-, PIK3CA+, advanced or metastatic
lapatinib (Tykerb)	Advanced or metastatic breast cancer
tucatinib (Tukysa)	Metastatic breast cancer
neratinib (Nerlynx)	Early breast cancer
	Advanced, metastatic breast cancer
elacestrant (Orserdu)	Breast cancer, HR+, HER2-, ESR1+, advanced or metastatic
capivasertib (Truqap)	Breast cancer, HR+, HER2-, PIK3CA/AKT1/PTEN+, advanced or metastatic

Policy Implementation/Update

Action and Summary of Changes	Date
Added a new indication for palbociclib (Ibrance) – first line treatment of metastatic or advanced breast cancer in combination with inavolisib (Itovebi) and fulvestrant (Faslodex).	02/2025
Removed Kisqali/Femara as it has been discontinued by the manufacturer. Reintroduced high-risk criteria for Verzenio in early breast cancer. Expanded criteria for high-risk disease for Kisqali in the setting of early breast cancer per NATALEE trial. Updated supporting evidence. Updated appendix. Updated related policies.	12/2024
Added expanded indication for Kisqali in the setting of early breast cancer. Removed high-risk criteria for Verzenio in early breast cancer. Added endocrine-based therapy as an adjuvant treatment option. Updated supporting evidence for monarchE trial, NATALEE trial, MAINTAIN trial. Updated references.	11/2024
Effective 01/01/2023 - Updated criteria in early breast cancer to allow coverage when Ki-67 <20% to align with definition of high-risk breast cancer NCCN/ASCO guidelines. Updated criteria requiring trial of Verzenio or Kisqali prior to Ibrance in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer due to new OS data from PALOMA-2 trial. Updated criteria formatting. Updated supporting evidence and references. Added related policies and appendix.	12/2022
Updated requirement of palbociclib (Ibrance) and abemaciclib (Verzenio) prior to Kisqali to an or, in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer.	10/2022
Added expanded indication for Abemaciclib (Verzenio) for adjuvant therapy of high-risk early stage breast cancer; added and rearranged relevant supporting information; updated policy to categorize adjuvant therapy for EBC vs systemic chemotherapy for advanced and metastatic breast cancer; aligned use of Verzenio and Ibrance in male population with current FDA approval and recommendations; removed specialist prescribing criteria for renewal; added split fill requirement for Verzenio	11/2021
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
Transitioned criteria to policy format and merged into one policy and added add step through abemaciclib (Verzenio) and palbociclib (Ibrance) for Kisqali, effective 1/1/2021.	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