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 (CDK4/6) 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)	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
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), ribociclib (Kisqali), and ribociclib/letrozole (Kisqali/Femara)** 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 CDK4/6 inhibitor (e.g. ribociclib [Kisqali], abemaciclib [Verzenio]); **AND**

D. Member has a diagnosis of hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer; **AND**
E. The request is for **adjuvant therapy of early-stage (stage I- III) breast cancer (EBC)**; **AND**
    1. Provider attests the member has high-risk breast cancer based on one the following:
        i. Histopathological tests showing four or more (≥ 4) axillary lymph nodes are affected (pALN N2 or N3 disease); **OR**
        ii. Histopathological tests showing one to three axillary lymph nodes are affected, and one of the following:
            a. Tumor size is ≥ 5 cm; **OR**
            b. Histopathological grade 3 disease (G3); **OR**
            c. The member has a Ki-67 score ≥ 20% as determined by an FDA-approved test; **AND**
    2. The member has undergone definitive surgical resection of the primary tumor; **AND**
    3. The member has received therapy using one of the following treatment modalities:
        i. Radiotherapy; **OR**
        ii. Taxane (e.g., docetaxel) and/or anthracycline (e.g., doxorubicin) based chemotherapy; **AND**
    4. The request is for abemaciclib (Verzenio); **AND**
        i. Abemaciclib (Verzenio) will be used in combination with aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or tamoxifen; **AND**
        ii. Will not be used in combination with any additional oncology therapy; **OR**
F. The request is for **systemic therapy of recurrent, advanced, or metastatic breast cancer**; **AND**
    1. Member has a diagnosis of advanced (stage III), or metastatic (stage IV) breast cancer; **AND**
    2. The medication is being prescribed as a first-line systemic therapy; **AND**
        i. The medication will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or fulvestrant; **AND**
        ii. Will not be used in combination with any additional oncology therapy; **AND**
        iii. The member is a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **OR**
            a. The member is hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); OR
    3. The medication is being prescribed in as a second-line systemic therapy; **AND**
        i. The medication 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 a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **OR**
a. The member is hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); **OR**

4. The medication is being prescribed for subsequent-line (3rd line or later) systemic therapy in metastatic (stage IV, M1) setting; **AND**
i. Member had disease progression on, or after endocrine therapy AND systemic chemotherapy (not containing a CDK 4/6 inhibitor) in the metastatic (stage IV) setting; **AND**
ii. 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. Adjuvant therapy of early stage breast cancer (palbociclib (Ibrance) and ribociclib (Kisqali))
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); **AND**

IV. 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):** Abemaciclib (Verzenio) was evaluated as a 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. Abemaciclib (Verzenio) was recently 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. As of Oct. 2021, IDFS data for 2,003 patients in cohort 1, who had Ki-67 scores ≥ 20% (1,017 in Verzenio arm and 986 in comparator ET arm) was reported, which exhibited significant improvement in IDFS for Verzenio over conventional endocrine therapy alone with a 36-month IDFS of 86.1% (82.8, 88.8) versus 79% (75.3, 82.3) (HR = 0.626; [95% CI, 0.48, 0.80]; *p*= 0.0042). Results published December 2022 from a preplanned interim analysis noted an increase in absolute invasive disease–free survival and distant recurrence–free survival benefit at 4 years benefit of abemaciclib (Verzenio), regardless of Ki-67 score. The overall survival (OS) data was immature.

i. While statistically significant improvements in IDFS for patients in cohort 1 with

Ki-67 score ≥ 20% at the final IDFS analysis was favorable for the indicated subpopulation, it was not favorable for the ITT population. Although OS data was immature, the ITT population observed hazard ratios for OS was 1.091 (95% CI, 0.818 to 1.455) and HR = 0.767 (95% CI, 0.511 to 1.152) in the FDA-approved population (cohort 1) appear to have influenced the label indication. The FDA labeled indication for adjuvant abemaciclib (Verzenio) was limited to the subset of patients with a worse prognostic risk on the basis of a higher anatomic stage (cohort 1) and with higher tumor proliferation based on Ki-67 biomarker expression (>20 %).

ii. As of December 2022, the NCCN guidelines for invasive breast cancer (version 4.2022) define high risk breast cancer as those with ≥ 4 positive lymph nodes, or 1–3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%), which is consistent with the inclusion criteria for MONARCH-E trial design. The guideline recommends two years of adjuvant therapy with abemaciclib (Verzenio) in combination with endocrine therapy in patients with HR+/HER2-, high-risk breast cancer that meet that definition, thus suggesting broader consideration of treatment than the FDA label.

iii. Furthermore, the American Society of Clinical Oncology (ASCO) has updated their guideline and is consistent with the NCCN guideline recommendation, in that adjuvant abemaciclib (Verzenio) may be offered to patients with either ≥ 4 positive lymph nodes (regardless of Ki-67 score) or 1-3 lymph nodes with high-risk features (grade 3 disease or tumor ≥ 5 cm or Ki-67 ≥ 20%) – in line with the definition/inclusion criteria of the MONARCH-E trial.

iv. Upon outreach to a key opinion leader specializing in oncology, practical considerations exist outside of using Ki-67 score as a sole marker for high-risk status in breast cancer. There are moderate quality data to suggest Ki-67 testing as an accepted clinical measure to guide therapy decisions for patients with early breast cancer; however analytical validity of Ki-67 testing remains poor. Analytical validity, standardization, and interobserver reproducibility have been cited as limitations of using this biomarker to drive patient-care decisions. There remain challenges in implementing Ki-67 scoring as a standard of care, and given individual circumstances such as when Ki-67 testing may not be readily available in situations where there is absence of tissue sample, and when all other criteria are met for patients that meet the definition of high-risk early breast cancer, treatment with adjuvant abemaciclib (Verzenio) may be appropriate.

b. 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.

c. 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.
    1. 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 plus fulvestrant and 37.3 months for placebo plus fulvestrant (hazard ratio [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.

d. 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. **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:

- 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).
- 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).

- 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.
- 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.
- 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).

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

- 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).

- MONALEESA-7: Ribociclib (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. 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).
- 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). 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.

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.

- Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) have received FDA-approval in the setting of treatment of breast cancer in men. For abemaciclib (Verzenio), this indication also extends in the adjuvant setting for the treatment of early breast cancer with high risk of recurrence.
- 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.
- In the preoperative/adjuvant therapy setting, chemotherapy with or without HER2-targetted therapy is recommended in male population. Typical adjuvant endocrine therapy option for men with breast cancer include tamoxifen, or, if tamoxifen is contraindicated, an aromatase inhibitor in combination with 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.
- 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 guideline 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. 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 NCCN notes a lack of data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen. As of December 2022, NCCN guidelines state, "If there is disease progression while on a CDK4/6 inhibitor, there is are limited data to support the use of another CDK4/6 inhibitor."

VIII. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, and exemestane. Chemotherapy regimens 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 the aforementioned criteria.

XI. As of December 2022, 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 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. As of December 2022, the 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) received FDA approval in the setting of adjuvant therapy of high-risk early stage breast cancer (EBC). Clinical trials are ongoing for palbociclib (Ibrance) and ribociclib (Kisqali). However, these agents have not been FDA approved in this setting.

Appendix

I. The tumor, node, metastasis (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. TX: Main tumor cannot be measured
      ii. T0: Main tumor cannot be found
      iii. 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

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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)	PIK3CA mutation, advanced or metastatic breast cancer
Lapatinib (Tykerb)	Advanced or metastatic breast cancer
Tucatinib (Tukysa)	Metastatic breast cancer
Neratinib (Nerlynx)	Early breast cancer
	Advanced, metastatic breast cancer

Policy Implementation/Update

Action and Summary of Changes	Date
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 formatting. Updated supporting evidence and references. Added related policies and appendix.	12/2022
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	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