Epidermal Growth Factor Receptor (EGFR); Tyrosine Kinase Inhibitors (TKI)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO023

Description
Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) are orally administered epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs).

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

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
osimertinib (Tagrisso)	Non-Small Cell Lung Cancer (NSCLC), resectable early stage with EGFR exon 19 or 21 L858R mutation; Non-Small Cell Lung Cancer (NSCLC), unresectable, stage III, with EGFR exon 19 or 21 L858R mutation Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation	40 mg tablets	30 tablets/30 days
		80 mg tablets	
dacomitinib (Vizimpro)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	15 mg tablets	30 tablets/30 days
		30 mg tablets	
		45 mg tablets	
generic erlotinib	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation; Pancreatic cancer, advanced or metastatic	25 mg tablets	90 tablets/30 days
		100 mg tablets	30 tablets/30 days
	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	150 mg tablets	30 tablets/30 days
erlotinib (Tarceva)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	25 mg tablets	90 tablets/30 days
		100 mg tablets	30 tablets/30 days

	Pancreatic cancer, advanced or metastatic		
	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	150 mg tablets	30 tablets/30 days
afatinib (Gilotrif)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	20 mg tablets	30 tablets/30 days
		30 mg tablets	
		40 mg tablets	
gefitinib (Iressa)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	250 mg tablets	30 tablets/30 days
generic gefitinib	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	250 mg tablets	30 tablets/30 days
lazertinib (Lazcluze)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation	80 mg tablet	60 tablets/30 days
		240 mg tablet	30 tablets/30 days

Initial Evaluation

I. **Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (generic Iressa), gefitinib (Iressa), and lazertinib (Lazcluze)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The medication will not be used in combination with any other oncology therapy unless outlined in policy; **AND**
      1. **The request if for osimertinib (Tagrisso); AND**
         i. The member has early stage (stage IB-IIIA) non-small cell lung cancer; **AND**
            a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
            b. The member has <u>not</u> had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
            c. The member has undergone complete tumor resection; **AND**
            d. The treatment will be used as adjuvant therapy; **AND**
            e. The member has been previously treated with platinum-based chemotherapy (e.g., cisplatin); **OR**
               i. Platinum-based chemotherapy (e.g., cisplatin) is contraindicated or not tolerated; **OR**

ii. The member has locally advanced, unresectable (stage III) non-small cell lung cancer; **AND**
   a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
   b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
   c. The member has not progressed during or following concurrent or sequential platinum-based chemoradiation; **OR**

iii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
   a. Treatment will be used in combination with pemetrexed and platinum-based chemotherapy; **OR**
      i. Medication will be used as monotherapy; **AND**
   b. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
      i. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
         1. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **OR**
      ii. Confirmation of epidermal growth factor receptor (EGFR) T790 mutation; **AND**
         1. Documented disease progression on previous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**

2. The request is for **dacomitinib (Vizimpro); AND**
   i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
   ii. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
   iii. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
   iv. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
   v. The member does not have brain metastases; **OR**
3. The request is for **erlotinib (Tarceva); AND**
   i. Generic erlotinib is prescribed; **OR**
      a. The member has tried and failed, has a contraindication to, or intolerance to generic erlotinib; **AND**

ii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
    a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
    b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
    c. The treatment will be used for first-line, maintenance, second-line, or greater-line treatment, and may have progressed after previous chemotherapy; **OR**

iii. The member has locally advanced, unresectable or metastatic (stage IV), pancreatic cancer; **AND**
    a. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
    b. Treatment will be used in combination with gemcitabine; **OR**

4. The request is for **afatinib (Gilotrif); AND**
    i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
        a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation, or L861Q, G719X, or S7681 mutation; **AND**
        b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
        c. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **OR**
            i. The member had disease progression on platinum-based chemotherapy (e.g., cisplatin, carboplatin, etc.); **OR**
    ii. Metastatic, squamous non-small cell lung cancer that has progressed on or after treatment with platinum-based chemotherapy (e.g., cisplatin, carboplatin, etc.)
5. The request is for **gefitinib (generic Iressa)** or **BRAND gefitinib (Iressa); AND**
    i. Generic gefitinib is prescribed; **OR**
        a. The member has tried and failed, has a contraindication to, or intolerance to generic gefitinib; **AND**
    ii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
        a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**

b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
c. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **OR**

6. The request is for **lazertinib (Lazcluze); AND**
   i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
   ii. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
   iii. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
   iv. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
   v. Treatment will be used in combination with amivantamab (Rybrevant)*; **AND**
      a. Provider attestation that prophylactic anticoagulation (e.g., apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran, enoxaparin, etc.) will be concomitantly administered for the first four months of treatment; **AND**
   vi. There are no evident central nervous system (CNS) metastases; **AND**
      a. Documentation of intolerance or contraindication to osimertinib (Tagrisso)*, erlotinib (Tarceva)*, gefitinib (Iressa)*, afatinib (Gilotrif)*, and dacomitinib (Vizimpro)*; **OR**
   vii. There are central nervous system (CNS) metastases; **AND**
      a. Documentation of intolerance or contraindication to osimertinib (Tagrisso)*

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

II. Dacomitinib (Vizimpro) is considered not medically necessary when criteria above are not met and/or when used for:
   A. The treatment of non-small cell lung cancer (NSCLC) in the second line setting

III. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) are considered investigational when used for all other conditions, including but not limited to:
   A. Dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) used in combination with any other treatment including chemotherapy or targeted agent
   B. Early-stage epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC) with agents other than osimertinib (Tagrisso)

C. Lazertinib (Lazcluze) monotherapy in non-small cell lung cancer (NSCLC) with T790M mutation
D. Lazertinib (Lazcluze) in non-small cell lung cancer (NSCLC) with mesenchymal epithelial transition factor receptor (MET) overexpression
E. Pancreatic cancer
F. Squamous non-small cell lung cancer (NSCLC)
G. Head and neck cancer
H. Renal cell carcinoma
I. Bone cancer including, but not limited to, chordoma
J. Central nervous system cancers without primary tumor source of non-small cell lung cancer (NSCLC)
K. Hepatobiliary cancers

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; **AND**
III. The medication will not be used in combination with any other agent listed in this policy, or another medication for the oncolytic condition being treated; **OR**
    - The request is for erlotinib (Tarceva) in combination with gemcitabine for the treatment of pancreatic cancer; **OR**
    - The request is for osimertinib (Tagrisso) in combination with platinum-based chemotherapy (e.g., cisplatin) for non-small cell lung cancer with EGFR exon 19 or 21 L858R mutation; **OR**
    - The request is for lazertinib (Lazcluze) in combination with amivantamab (Rybrevant)* for non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
IV. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
V. If the request is for brand erlotinib (Tarceva), generic erlotinib has not been tolerated or is contraindicated; **OR**
VI. If the request is for brand gefitinib (Iressa), generic gefitinib has not been tolerated or is contraindicated

Supporting Evidence

I. Lung cancer is the second most common cancer diagnosed in the U.S. and is the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) represents up to 85% of lung cancer diagnoses and EGFR mutations occur in up to one-third of patients with NSCLC. Epidermal

growth factor receptor exon 19 deletions or exon 21 L858R substitution mutations make up around 90% of all EGFR mutations.

II. Given the complexity of management of NSCLC and pancreatic cancer, the treatment of NSCLC and pancreatic cancer must be initiated by, in or consultation with, an oncologist.

III. The National Comprehensive Cancer Network (NCCN) guidelines for treatment of Non-Small Cell Lung Cancer have been updated to include lazertinib (Lazcluze) in combination with amivantamab (Rybrevant). The National Cancer Center Network (NCCN) recommends osimertinib (Tagrisso) monotherapy (category 1, preferred), osimertinib (Tagrisso) with chemotherapy, and lazertinib (Lazcluze) in combination with amivantamab (Rybrevant) (category 1, other recommendation) as first line therapy in patients who have EGFR exon 19 deletion or exon 21 L858R mutations. The National Cancer Center Network (NCCN) guidelines also note erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) monotherapy may be useful in certain circumstances in the first line setting (category 1).

Osimertinib (Tagrisso)

IV. Osimertinib (Tagrisso) is FDA-approved for treatment of early stage (IIB-IIIA) NSCLC with exon 19/21 L858R mutation as adjuvant therapy after complete tumor resection, treatment of stage III, unresectable NSCLC with exon 19/21 mutation after completion of chemoradiation, in the first line setting for metastatic NSCLC with exon 19/21 L858R mutation (with or without platinum-based chemotherapy), and in the second-line setting for metastatic NSCLC with T790M mutation.

- Osimertinib (Tagrisso) was studied in the FLAURA trial, which included 556 treatment naïve participants with EGFR NSCLC. Osimertinib (Tagrisso) was compared to gefitinib or erlotinib. Osimertinib (Tagrisso) demonstrated improvement in progression free survival (PFS), median PFS 18.9 months vs 10.2 months in the osimertinib (Tagrisso) arm vs gefitinib/erlotinib, hazard ratio (HR) 0.46 (95% CI, 0.37 to 0.57, P<0.001). Mature overall survival (OS) was in favor of osimertinib (Tagrisso) compared to gefitinib/erlotinib, 38.6 months vs 31.8 month, HR 0.8 (95% CI, 0.64 to 1, P=0.046). The safety profile was favorable compared to studied EGFR TKIs. Osimertinib (Tagrisso) showed greater intracranial efficacy and tolerability.
- Tumors that progress on TKIs are found to have a substitution of methionine for threonine at position 790 (T790M) mutation on exon 20. Osimertinib (Tagrisso) has been demonstrated to have efficacy in patients with this mutation. Currently, there is no evidence for safety or efficacy in the second line setting for osimertinib (Tagrisso) in absence of this mutation and the medication shall not be used.
- Osimertinib (Tagrisso) demonstrated disease free survival for patients with stage IB-IIIA disease NSCLC with exon 19-21 mutation in the Phase 3 (ADAURA) trial. Mature OS data was in favor of osimertinib (Tagrisso) compared to placebo, HR 0.17 (95% CI, 0.11 to 0.26); P < 0.001. Patients were excluded from the trial if they had received any prior EGFR-TKI therapy. Safety of osimertinib (Tagrisso) in this population is unknown, and efficacy would not be expected in this setting after progression on another agent within the same class. All patients had the EGFR exon

19 or exon 21 L858R mutation, and all patients had undergone complete (negative margins) surgical resection of NSCLC tumors. The majority of patients (76%) with stage II-IIIA disease had received previous adjuvant platinum-based chemotherapy, as well as 25% of those with stage IB disease (53% had received prior platinum therapy overall). Use of previous platinum-based chemotherapy is not required by the FDA-approved indication; however, NCCN guidelines make a category 1 recommendation for osimertinib (Tagrisso) as adjuvant therapy for treatment of stage IB-IIIA NSCLC with exon 19-21 mutation after receiving previous adjuvant chemotherapy or in patients that are ineligible to receive platinum-based chemotherapy.

- In the Phase 3, double-blind, placebo-controlled trial (LAURA), osimertinib (Tagrisso) demonstrated significantly longer progression-free survival than placebo in patients with unresectable stage III *EGFR*-mutated NSCLC who had not progressed during or following concurrent or sequential platinum-based chemoradiation, 39.1 vs 5.6 months, PFS HR 0.16 (95% CI, 0.10 to 0.24; P<0.001). Interim OS data (maturity, 20%) showed 36-month overall survival among 84% of patients with osimertinib (95% CI, 75 to 89) and 74% with placebo (95% CI, 57 to 85), with a HR for death of 0.81 (95% CI, 0.42 to 1.56; P=0.53). The most common adverse events, irrespective of cause, were radiation pneumonitis (48% with osimertinib vs. 38% with placebo), diarrhea (36% vs. 14%), and rash (24% vs. 14%). Adverse events of grade 3 or higher were reported in 50 patients (35%) with osimertinib and 9 patients (12%) with placebo. PFS and ORR endpoints are surrogate markers that do not directly measure clinical outcomes that predict morbidity or mortality. OS was not yet matured at PFS read out but no trend towards a detriment was observed. PFS is a surrogate endpoint and TKI studies have not demonstrated a strong positive correlation between PFS and OS in NSCLC with EGFR mutation and the quality of evidence is considered low.
- The Phase 3, open-label, randomized trial (FLAURA2) evaluated efficacy of osimertinib (Tagrisso) plus platinum-based chemotherapy versus osimertinib (Tagrisso) monotherapy, in treatment of patients with advanced or metastatic NSCLC with exon 19-21 L858R mutation who had not previously received treatment for advanced disease. A total of 557 participants were randomized 1:1 (stratified by race) to receive osimertinib (80 mg once daily) with chemotherapy (pemetrexed [500 mg per square meter of body-surface area] plus either cisplatin [75 mg per square meter] or carboplatin [pharmacologically guided dose]) or to receive osimertinib monotherapy (80 mg once daily). Participants were 18 years and older and central nervous system (CNS) metastases were permitted if neurologically stable. The median age was 61 years, 61% were female; 64% were Asian and 66% were never smokers. Osimertinib (Tagrisso) plus platinum-based chemotherapy demonstrated a significantly longer PFS compared to osimertinib (Tagrisso) monotherapy HR 0.62 (95% CI, 0.49 to 0.79, p<0.001). OS was not mature at PFS data cutoff but favored the osimertinib (Tagrisso) plus chemotherapy group

compared to osimertinib (Tagrisso) monotherapy, 79% (95% CI, 73 to 83) and 73% (95% CI, 67 to 78). Adverse events of grade 3 or higher were reported in 176 patients (64%) in the osimertinib–chemotherapy group and in 75 (27%) in the osimertinib group. The most common adverse events were anemia, diarrhea, nausea, and decreased appetite. There is uncertainty in the clinical meaningfulness of PFS as it is a surrogate endpoint that has not been correlated with clinically meaningful outcomes such as morbidity and mortality in NSCLC with EGFR mutations. The quality of evidence is considered low due to the lack of blinding and use of surrogate endpoints.

Dacomitinib (Vizimpro)

V. Dacomitinib (Vizimpro) is FDA-approved for the treatment of adults with metastatic non-small cell lung cancer with EGFR exon 19 or 21 deletion mutation.

VI. The efficacy and safety of dacomitinib (Vizimpro) was demonstrated in an open-label trial that assessed dacomitinib (Vizimpro) in the first-line, metastatic disease, treatment naïve, monotherapy setting. Patients were excluded if they had previous use of another EGFR TKI and/or presence of brain metastases. Dacomitinib (Vizimpro) was compared against gefitinib (Iressa), and showed an improvement in PFS.

VII. Dacomitinib (Vizimpro) has been studied in the second-line setting, as well as in non-small cell lung cancer with undetermined mutational status; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.

Erlotinib (Tarceva)

VIII. Erlotinib (Tarceva) was evaluated in the OPTIMAL, EURTAC, and ENSURE trials versus chemotherapy. Objective response rates (ORR) and PFS were favorable for erlotinib (Tarceva).

IX. Erlotinib (Tarceva) was evaluated in combination with gemcitabine for pancreatic cancer. Results of phase III studies have indicated an increase in survival compared to gemcitabine alone; however, grade I and II adverse events are expected to occur at greater frequency with combination therapy.

Afatinib (Gilotrif)

X. Afatinib (Gilotrif) was evaluated in the LUX clinical trials program versus chemotherapy and showed an increase in PFS as well as time to symptom progression and quality of life. Afatinib (Gilotrif) is also FDA-approved for S761I, L861Q, and G719X mutations.

XI. Afatinib (Gilotrif) was evaluated in an RCT versus erlotinib (Tarceva) for previously treated, metastatic, squamous NSCLC. The results were favorable for afatinib (Gilotrif) over erlotinib (Tarceva) in PFS and OS.

Gefitinib (Iressa)

XII. Gefitinib (Iressa) showed favorable PFS against chemotherapy in several RCTs.

XIII. Treatment of EGFR TKI for NSCLC shall be individualized based on provider and patient preferences, and disease characteristics. There have been several trials comparing agents in this policy. Gefitinib (Iressa) has shown comparable efficacy to erlotinib (Tarceva) and afatinib (Gilotrif) and may modestly improve outcomes over gefitinib (Iressa); however, it may increase risk of serious toxicities as well.

XIV. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Lazertinib (Lazcluze)

XV. Lazertinib (Lazcluze) was studied in a Phase 3, randomized study (MARIPOSA). The study included 1,074 participants 18 years and older with confirmed locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Participants were treatment naïve for advanced disease and randomized to receive lazertinib (Lazcluze) 240mg daily plus amivantamab (Rybrevant) 1050mg (if <80kg) or 1400mg (if >80kg) intravenously once weekly for five weeks, then every two weeks, osimertinib (Tagrisso) 80mg daily, or lazertinib (Lazcluze) 240mg daily. The lazertinib (Lazcluze) combination arm was unblinded while the osimertinib (Tagrisso) and lazertinib (Lazcluze) arms were blinded. Baseline characteristics were similar between both groups: median age 63 years, mostly female (60%), 89% Asian, 41% brain metastases, 60% exon 19 deletion, and 40% exon 21 L858R mutation. The primary endpoint of progression free survival (PFS) was statistically significant, favoring the lazertinib (Lazcluze) plus amivantamab (Rybrevant) group compared to osimertinib (Tagrisso), 23.7 months vs 16.6 months, difference of 7.1 months, HR 0.70 (0.58-0.85), p <0.001. Overall survival was not mature at the time of PFS readout. Objective response rate was 86% vs 85% in the lazertinib (Lazcluze) plus amivantamab (Rybrevant) group vs osimertinib (Tagrisso). Recent study updates from May 2024 provided by the FDA demonstrate that OS is trending in favor of lazertinib (Lazcluze) in combination with amivantamab (Rybrevant), HR 0.77 (95% CI, 0.61-0.96) at 82% maturity, compared to osimertinib (Tagrisso). However, interim OS data is considered descriptive. The quality of evidence is considered low due to the lack of blinding and use of surrogate endpoints. It is unknown how lazertinib (Lazcluze) in combination with amivantamab (Rybrevant) compares to other osimertinib (Tagrisso) with chemotherapy or other TKIs.

1. Lazertinib (Lazcluze) demonstrated significantly more adverse events compared to osimertinib (Tagrisso). Grade 3 or higher adverse events were reported in 75% of the patients treated with lazertinib (Lazcluze) plus amivantamab (Rybrevant) and in 43% of those treated with osimertinib (Tagrisso). Paronychia (11% vs <1%) and rash (15% vs 1%) were the most common adverse events. Venous thromboembolism (VTE) adverse events were reported in 37% of the patients in the lazertinib (Lazcluze) plus amivantamab (Rybrevant) arm and in 9% of those in the osimertinib (Tagrisso) arm.

XVI. The National Comprehensive Cancer Network (NCCN) guidelines recommend osimertinib (Tagrisso) monotherapy as a preferred first-line regimen compared to lazertinib (Lazcluze) plus amivantamab (Rybrevant) (both category 1). The National Comprehensive Cancer Network (NCCN) also makes a category 1 recommendation for erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) as first line treatment for NSCLC with exon 19/21

mutation. In the absence of direct comparison data demonstrating inferiority of specific EGFR TKIs, for lazertinib (Lazcluze), requiring treatment with osimertinib (Tagrisso), erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) in members with no CNS involvement, is clinically appropriate and cost effective. Guidelines acknowledge that osimertinib (Tagrisso) and lazertinib (Lazcluze) have brain-penetrant properties, as such treatment with osimertinib (Tagrisso) is required for members presenting with CNS metastases.

Investigational or Not Medically Necessary Uses

I. Dacomitinib (Vizimpro) was evaluated versus placebo and erlotinib (Tarceva) in the second-line setting; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.
II. The agents in this policy have not been sufficiently evaluated in the following settings. Some data may be available or may be recommended by NCCN; however, safety and efficacy have not been established:
    A. Dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) used in combination with any other treatment including chemotherapy or targeted agent
    B. Early stage epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC)outside of osimertinib (Tagrisso)
    C. Lazertinib (Lazcluze) monotherapy in non-small cell lung cancer (NSCLC) with T790M mutation
    D. Lazertinib (Lazcluze) in non-small cell lung cancer (NSCLC) with mesenchymal epithelial transition factor receptor (MET) overexpression
    E. Pancreatic cancer
    F. Squamous non-small cell lung cancer (NSCLC)
    G. Head and neck cancer
    H. Renal cell carcinoma
    I. Bone cancer including, but not limited to, chordoma
    J. Central nervous system cancers without primary tumor source of non-small cell lung cancer (NSCLC)
    K. Hepatobiliary cancers

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added lazertinib (Lazcluze) to policy and updated QL table to detail specific indications. Included a path to coverage for osimertinib (Tagrisso) in combination with platinum-based chemotherapy for first line	02/2025

treatment of NSCLC with exon 19/21 L858R. Added criteria for osimertinib (Tagrisso) in stage III, unresectable, NSCLC with EGFR exon 19/21 mutation, after chemoradiation. Updated format of criteria.	
Added generic erlotinib to QL table	01/2024
Added gefitinib (generic Iressa) to the policy; required step through generic gefitinib prior to use of branded Iressa; updated to match current policy formatting	07/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy updated to include osimertinib (Tagrisso) indication of early stage, adjuvant treatment to surgical resection in NSCLC.	01/2021
Criteria update and policy creation: All EGFR TKI agents combined into one policy, streamline quantity limits, renewal criteria, duration or approval upon initial and renewal request. Update Tagrisso criteria to allow for use in the first line setting. Addition of age requirement and prescriber requirement for all agents.	07/2019
Gilotrif criteria update: updated criteria to include L861Q, G719X, or S768I mutations and metastatic, squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. Due to the statement that afatinib is not recommended as second-line therapy for squamous cell carcinoma from National Comprehensive Cancer Network (NCCN), a clinical note has been added to address the request for afatinib in members who are diagnosed with squamous NSCLC that has progressed on platinum-based chemotherapy. Tagrisso criteria update: Include clinical note regarding the Flaura trial and recent NCCN NSCLC Guidelines. Also, a route for approval if patient has a contraindication to erlotinib, afatinib and gefitinib.	03/2018
Gilotrif criteria update: updated criteria to new format, deleted renal and hepatic function questions, and deleted female contraception questions as this is properly managed by providers	01/2018
Previous reviews	12/2015, 01/2015, 09/2013, 05/2013, 11/2012, 03/2012, 03/2012, 10/2008, 04/2007
Criteria created	09/2005