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), and gefitinib (Iressa) are orally administered epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs).

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

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
osimertinib (Tagrisso)	40 mg tablets	NSCLC	30 tablets/30 days
	80 mg tablets		
dacomitinib (Vizimpro)	15 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	45 mg tablets		
erlotinib (Tarceva)	25 mg tablets	NSCLC; Pancreatic cancer	90 tablets/30 days
	100 mg tablets		30 tablets/30 days
	150 mg tablets	NSCLC	30 tablets/30 days
afatinib (Gilotrif)	20 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	40 mg tablets		
gefitinib (Iressa)	250 mg tablets	NSCLC	30 tablets/30 days

Initial Evaluation

I. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), and gefitinib (Iressa) 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 agent listed in this policy, or another medication for the condition being treated unless outlined specifically below; **AND**
D. Criteria below are met for the specific agent requested;
    1. **For osimertinib (Tagrisso)**
        i. Non-small cell lung cancer, early stage IB-IIIA; **AND**
            a. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **AND**
            b. The member has not had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
            c. Osimertinib (Tagrisso) will be used as adjuvant therapy after the member has undergone complete surgical resection of the tumor; **AND**
            d. The member has been previously treated with, or is ineligible to receive, platinum-based chemotherapy (e.g., cisplatin); **OR**
        ii. Locally advanced unresectable or metastatic (stage IV) non-small cell lung cancer being treated for ONE of the following (a or b):
            a. First-line treatment in the metastatic setting that has NOT progressed while using another EGFR TKI; **AND**
                i. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **OR**
            b. After disease progression on another EGFR TKI; **AND**
                i. The tumor is documented to be EGFR T790 mutation-positive
    2. **For dacomitinib (Vizimpro)**
        i. Metastatic (stage IV) non-small cell lung cancer; **AND**
        ii. The member has not had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
        iii. The treatment will be used for first-line treatment in the metastatic setting (i.e., the member has not received ANY other therapy in the metastatic setting, including, but not limited to, chemotherapy); **AND**
        iv. The member does **NOT** have brain metastases; **AND**
        v. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated
    3. For erlotinib (Tarceva)
        i. Generic erlotinib is prescribed; **OR**

a. the member has tried and failed, has a contraindication to, or intolerance to generic erlotinib; **AND**

ii. Use is for one of the following (a or b):

a. Locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**

i. The member has not had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**

ii. The treatment will be used for first-line, maintenance, second-line, or greater-line treatment, and may have progressed after previous chemotherapy; **AND**

iii. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **OR**

b. A diagnosis of locally advanced, unresectable or metastatic (stage IV), pancreatic cancer; **AND**

i. The treatment will be used for first-line treatment in the locally advanced or metastatic setting; **AND**

ii. The medication will be used in combination with gemcitabine

4. For afatinib (Gilotrif)

i. Metastatic (stage IV) non-small cell lung cancer; **AND**

a. The member has not had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**

b. The treatment will be used for first-line treatment in metastatic setting; **AND**

c. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated, or has L861Q, G719X, or S7681 mutation; **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. For gefitinib (Iressa)

i. Metastatic (stage IV) non-small cell lung cancer; **AND**

ii. The member has not had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**

iii. The treatment will be used for first-line treatment in the locally advanced or metastatic setting; **AND**

iv. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated

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

III. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), and gefitinib (Iressa) are considered investigational when used for all other conditions, including but not limited to:
   A. When used in combination with any other treatment including chemotherapy or targeted agent
   B. Early stage EGFR NSCLC with agents other than osimertinib (Tagrisso), pancreatic cancer, squamous NCCLC
   C. Head and neck cancer
   D. Renal cell carcinoma
   E. Bone cancer including, but not limited to, chordoma
   F. Central nervous system cancers without primary tumor source of NSCLC
   G. Hepatobiliary cancers

Renewal Evaluation

I. The medication is prescribed by or in consultation with an oncologist; **AND**
II. 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**
   A. The request is for erlotinib (Tarceva) in combination with gemcitabine for the treatment of pancreatic cancer; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. If the request is for brand erlotinib (Tarceva), generic erlotinib has been ineffective, contraindication, or not tolerated.

Supporting Evidence

I. Osimertinib (Tagrisso) is FDA-approved in the first and second line setting for metastatic NSCLC depending on mutation characteristics. The FLAURA trial included 556 treatment naïve participants with EGFR NSCLC and was compared to gefitinib or erlotinib. Osimertinib (Tagrisso) demonstrated improvement in progression free survival (PFS). Although a surrogate outcome, overall survival (OS) is still being collected and the safety profile was favorable compared to other EGFR TKIs. Osimertinib (Tagrisso) showed greater intracranial efficacy and tolerability.
II. Tumors that progress on TKIs are found to have a substitution of methionine for threonine at position 790 (T790M) mutation, the only treatment with evidence in this setting is osimertinib

(Tagrisso). 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.

III. Osimertinib (Tagrisso) was subsequently FDA-approved for early stage (IB-IIIA), EGFR exon 19 deletion or 21 L858R mutated NSCLC as an adjuvant therapy to surgical tumor resection. In the Phase 3 (ADAURA) trial osimertinib (Tagrisso) demonstrated disease free survival for patients with stage IB-IIIA disease. At the time of reporting, the OS and quality of life data were immature. 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, platinum-based chemotherapy has been an established treatment for this stage of disease and is recommended over oral therapy in treatment guidelines and has a more established safety and efficacy profile (e.g., data are available to indicate OS with this therapy). Therefore, use of platinum-based chemotherapy is often the more appropriate and established treatment option, unless it has not been tolerated, patients are ineligible, or are contraindicated.

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

II. 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; however, this has unknown correlation to overall survival or quality of life parameters in NSCLC at this time.

III. 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.

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

V. 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.

VI. 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.

VII. 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.

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

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. When used in combination with other treatments (e.g., chemotherapy or targeted agent)
    B. Early stage EGFR NSCLC outside of osimertinib (Tagrisso), pancreatic cancer, squamous NCCLC
    C. Head and neck cancer
    D. Renal cell carcinoma
    E. Bone cancer including, but not limited to, chordoma
    F. Central nervous system cancers without primary tumor source of NSCLC
    G. Hepatobiliary cancers

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
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