**Medication Policy Manual**

**Policy No:** dru317  
**Topic:** Gilotrif®, afatinib  
**Date of Origin:** September 16, 2013  
**Committee Approval Date:** September 8, 2017  
**Next Review Date:** June 2018  
**Effective Date:** October 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Afatinib (Gilotrif) is an oral cancer medication used in the treatment of metastatic non-small cell lung cancer (NSCLC) when specific genetic mutations are present.
Policy/Criteria

I. Most contracts require prior authorization approval of afatinib (Gilotrif) prior to coverage. Afatinib (Gilotrif) may be considered medically necessary when criterion A or B below is met.

A. A diagnosis of metastatic (stage IV) non-small cell lung cancer (NSCLC) when criteria 1, 2, AND 3 are met.
   1. Documentation of an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation is provided. [refer to Medical Policy Genetic Testing 56, ‘Molecular Analysis for Targeted Therapy of NSCLC’] AND
   2. The patient has had no prior cytotoxic or targeted chemotherapy for NSCLC.
   AND
   3. Afatinib (Gilotrif) is used as monotherapy.

OR

B. A diagnosis of metastatic (stage IV), squamous NSCLC when criteria 1 AND 2 are met.
   1. There is progression of disease after at least four cycles of a platinum-containing chemotherapy regimen.
   AND
   2. Afatinib (Gilotrif) is used as monotherapy.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers afatinib (Gilotrif) to be a self-administered medication.

B. When prior authorization is approved, afatinib (Gilotrif) may be authorized in quantities of up to 30 tablets per month.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Afatinib (Gilotrif) is considered investigational when given concomitantly with any other cytotoxic or targeted chemotherapy medication.

IV. Afatinib (Gilotrif) is considered investigational when used for all other conditions, including but not limited to:

A. Breast cancer
B. Colorectal cancer
C. Squamous cell carcinoma of the head and neck (SCCHN)
Position Statement

- Afatinib (Gilotrif) is an oral tyrosine kinase inhibitor (TKI) approved for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) when specific epidermal growth factor receptor (EGFR) mutations are present; and metastatic, squamous NSCLC that has progressed after platinum-based chemotherapy.

- In EGFR-mutated NSCLC, afatinib (Gilotrif) improved progression-free-survival (PFS) relative to platinum-based chemotherapy when used as a first-line monotherapy for metastatic disease in the presence of exon 19 deletions or exon 21 (L858R) substitution mutations. Overall survival (OS) between the two groups was similar.

- In previously treated, metastatic squamous NSCLC, afatinib (Gilotrif) improved median OS by approximately one month relative to erlotinib (Tarceva); however, it is not likely that this small difference is clinically relevant. Afatinib (Gilotrif) has not been compared with programmed death receptor-1 (PD-1) inhibitors, which have since become the standard of care in this setting.

- EGFR TKIs [afatinib (Gilotrif), erlotinib (Tarceva), and gefitinib (Iressa)] have become the standard of care for first-line metastatic EGFR-mutated NSCLC because they appear to have a similar beneficial effect on survival as platinum-based therapies, but are generally better tolerated.

- Afatinib (Gilotrif) and other EGFR TKIs have not been adequately evaluated in NSCLC tumors with genetic mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations. Tumors with the T790M or S768I mutations are resistant to afatinib (Gilotrif), gefitinib (Iressa), and erlotinib (Tarceva).

- Afatinib (Gilotrif) has not been shown to provide a benefit when used in combination with chemo- or immunotherapies, or in other types of cancer.

- Common adverse effects (AEs) reported with afatinib (Gilotrif) include diarrhea, rashes and acne, mouth sores, decreased appetite, and itching. Dose adjustments or interruption of therapy may be necessary if AEs are severe.

- The usual dose of afatinib (Gilotrif) is 40 mg (one tablet) orally once daily. The safety and effectiveness of higher doses has not been studied.

Clinical Efficacy

METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

- Two, low quality, open-label, randomized controlled trials (RCTs) studied afatinib (Gilotrif) in patients with metastatic NSCLC as a first-line therapy when specific EGFR mutations were present.

  * Patients included in the trial had an activating mutation of EGFR (exon 19 deletion or exon 21 (L858R) substitution mutation), good performance status (ECOG performance status of 0 or 1), and adequate kidney and liver function.[1-3]

  * Afatinib (Gilotrif) was compared with a cisplatin chemotherapy doublet.[1-3]

  * The studies evaluated progression-free survival (PFS) as the primary endpoint. The median PFS reported for afatinib (Gilotrif) was consistent across both studies (11 months). The absolute difference in PFS was 4 to 5.5 months in favor of afatinib (Gilotrif).[1-3]
PFS is an intermediate endpoint which has not been found to accurately predict overall survival (OS) in the metastatic NSCLC setting. Median OS, a secondary endpoint, was not yet mature at the time of the initial PFS analysis. A subsequent updated survival analysis of these trials found no difference in OS with afatinib (Gilotrif) relative to therapy with a platinum-based chemotherapy, suggesting that there is a similar clinical benefit with the two therapies in EGFR-mutated metastatic NSCLC. This is consistent with OS results observed with the other EGFR TKIs.

Crossover to second- and third-line NSCLC therapies occurred in both treatment arms. This has occurred in all first-line NSCLC trials and may limit the accuracy with which a survival advantage can be measured.

A primary weakness of the studies included lack of blinding. In addition, one study had a large differential attrition of subjects which can erode randomization, while the other was conducted in Asia where standards of care differ from the U.S. which limits the generalizability of the results.

A large, open-label, pivotal trial [LUX-Lung 8] compared afatinib (Gilotrif) with erlotinib (Tarceva) in the second-line treatment of advanced, squamous NSCLC. Subjects had unresectable (stage IIIB) or metastatic (stage IV) NSCLC of squamous or mixed histology and had progression of disease after prior therapy with a platinum-based chemotherapy doublet (at least four cycles) in the first-line treatment setting.

Afatinib (Gilotrif) was statistically superior to erlotinib (Tarceva) with regard to median PFS and median OS; however, the difference was not clinically relevant (a 0.7 month and 1.1 month difference, respectively).

Afatinib (Gilotrif) has not been compared with programmed death receptor-1 (PD-1) inhibitor therapy, which has become the standard of care in the second-line treatment of metastatic, squamous NSCLC.

Because so few subjects with unresectable (stage IIIB) disease were enrolled in the clinical trial, the new FDA indication was only written to include the population with metastatic (stage IV) disease.

Afatinib (Gilotrif) has not been directly compared with erlotinib (Tarceva) or gefitinib (Iressa), two similar TKIs also used as a first-line treatment in metastatic NSCLC when these specific EGFR mutations are present.

The National Comprehensive Cancer Network (NCCN) NSCLC guideline lists afatinib (Gilotrif), gefitinib (Iressa), and erlotinib (Tarceva) as a category 1 recommendations for first-line treatment of metastatic NSCLC when activating EGFR mutations are detected. Platinum doublets are listed as category 1 recommendations for first-line treatment of metastatic NSCLC when tumors are negative for EGFR mutations or ALK translocations, or EGFR/ALK status is unknown. Afatinib (Gilotrif) is currently not listed on the guideline as an option for progressive metastatic squamous NSCLC.

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.
OTHER CANCER SETTINGS AND CONDITIONS
Because of its mechanism of action, there has been interest in studying afatinib (Gilotrif) in cancers other than NSCLC. Areas where afatinib (Gilotrif) has been studied but has not been found to improve clinical outcomes include metastatic squamous cell cancer of the head and neck (SCCHN) [8], metastatic colorectal cancer [9], breast cancer with brain metastasis [10], and in patients with advanced NSCLC who had progressed on erlotinib (Tarceva), gefitinib (Iressa), or both (LUX-Lung 4 trial). [11]

Safety
- Common (> 20% incidence) adverse reactions (AEs) experienced by patients taking afatinib (Gilotrif) in clinical trials include diarrhea, rash and acne, mouth sores, nail infections, dry skin, decrease in appetite, and itching. [12]
- Rare but serious AEs with afatinib (Gilotrif) include severe diarrhea, bullous and exfoliative skin disorders, interstitial lung disease, hepatotoxicity, and keratitis. [12]
- Dose reduction is recommended when afatinib (Gilotrif) is administered concomitantly with P-glycoprotein inhibitors (e.g. ritonavir, cyclosporine, erythromycin, verapamil, ketoconazole). [12]

Dosing
- The usual dose of afatinib (Gilotrif) is 40 mg (one tablet) orally once per day until progression of disease. The safety and effectiveness of higher doses has not been established. [12]
- The dose of afatinib (Gilotrif) may be modified if the usual dose is not tolerated. [12]
**Cross References**

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<thead>
<tr>
<th>Molecular Analysis for Targeted Therapy of NSCLC, Medical Policy Manual, Genetic Testing Policy No. 56</th>
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<td>Cycle Management Program, Medication Policy Manual, Policy No. dru404</td>
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**Codes**

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<th>Description</th>
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<tr>
<td>HCPCS</td>
<td>J8999</td>
<td>Oral chemotherapeutic drug, not otherwise classified</td>
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<td>ICD-10</td>
<td>C33, C34.00 – 34.02, C34.10 – C34.12, C34.20, C34.30 – C34.32, C34.80 – C34.82, C34.90 – C34.92, Z85.118</td>
<td>Non-small cell lung cancer</td>
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References


Revision History

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<th>Revision Date</th>
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<tr>
<td>9/8/2017</td>
<td>No changes to coverage criteria with this annual update.</td>
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<tr>
<td>9/9/2016</td>
<td>Coverage criteria for progressive, metastatic, squamous NSCLC were added with this annual update (a newly-approved FDA indication).</td>
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