PDL NEW DRUG REVIEW

Proprietary Name: Gilotrif®
Common Name: afatinib
PDL Category: Tyrosine Kinase Inhibitor

Comparable Products	Preferred Drug List Status
Tarceva	Recommended

Summary

Indications and Usage: For the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety and efficacy of Gilotrif® have not been established in patients whose tumors have other EGFR mutations. Females of reproductive ability should be counseled on pregnancy prevention during Gilotrif® treatment. They should also be advised to use highly effective contraception during treatment and for at least 2 weeks after the last dose of Gilotrif®. This is a pregnancy category D medication. The safety and efficacy of use in children have not been established.

Drug Interactions: The concomitant use of Gilotrif® with a P-glycoprotein (P-gp) inhibitor (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) can increase the exposure to afatinib. In those who must take a P-gp inhibitor, reduce the dose of Gilotrif® by 10mg per day if not tolerated. The concomitant use of Gilotrif® with a P-gp inducer (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort) can decrease the exposure to afatinib. In those taking a P-gp inducer, increase the dose of Gilotrif® by 10mg daily as tolerated.

Dosage Forms: Tablets, Film-Coated: 20mg, 30mg, 40mg

Recommended Dosage: The presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens should be verified by FDA-approved testing prior to the administration of this treatment. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC can be found at http://www.fda.gov/CompanionDiagnostics. Once detected, the recommended dose is 40mg once daily until disease progression or no longer tolerated. The dose should be taken at least 1 hour before or 2 hours after a meal.

The Gilotrif® dose should be withheld for any of the following drug-related adverse reactions: NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Grade 3 or higher; diarrhea of ≥Grade 2 persisting for ≥2 consecutive days while taking anti-diarrheal medication; cutaneous reactions of Grade 2 that are prolonged (>7 days) or intolerable; renal dysfunction ≥Grade 2. If begin treatment with Gilotrif® again, take at a reduced dose (i.e. 10mg per day less than the dose at which the adverse reaction occurred).

If patients require a P-glycoprotein (P-gp) inhibitor, reduce the dose of Gilotrif® by 10mg per day if not tolerated. If patients are taking a P-gp inducer, increase the dose of Gilotrif® by 10mg as tolerated. (See Drug Interactions section for further details).

Gilotrif® treatment should be permanently discontinued for: life-threatening bullous, blistering, or exfoliative skin lesions; confirmed interstitial lung disease; severe drug-induced hepatic impairment; persistent ulcerative keratitis; symptomatic left ventricular dysfunction; or severe/intolerable adverse reactions occurring at a dose of 20mg daily.

Dosing adjustments are not required for those with mild renal impairment. Closely monitor patients with moderate to severe renal impairment. Note that Gilotrif® has not been studied in those with severe renal impairment. Dosing adjustments are not required in those with mild or moderate hepatic impairment. Gilotrif® has not been studied in those with severe hepatic impairment, so closely monitor when used in this population and adjust the dose if not tolerated.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Gilotrif®) minus reported % incidence for comparator (pemetrexed/cisplatin).* The most commonly reported adverse events with Gilotrif® include diarrhea (73%), stomatitis (56%), cheilitis (11%), rash/dermatitis acneiform (79%), pruritus (20%), dry skin (29%), paronychia (58%), cystitis (8%), decreased appetite (0%), epistaxis (15%), rhinorrhea (5%), weight investigations (3%), pyrexia (6%), and conjunctivitis (8%). Laboratory abnormalities included alanine aminotransferase increased (7%), hypokalemia (6%), and aspartate aminotransferase increased (6%).

Diarrhea occurred in 96% of those treated with Gilotrif®, of which 15% was Grade 3 severity and occurred within the first 6 weeks of treatment. Renal impairment due to diarrhea also occurred during Gilotrif® treatment. This occurred in 6.1% of those treated with Gilotrif®, out of which 1.3% were Grade 3. It is recommended to withhold Gilotrif® treatment in those who develop Grade 2 diarrhea lasting >48 hours or in those who develop ≥Grade 3 diarrhea. Treatment should be withheld until the diarrhea resolves to ≤Grade 1. An anti-diarrheal agent may be taken at the onset of diarrhea.

Contraindications: There are currently no contraindications listed in the prescribing information.

Manufacturer: Boehringer Ingelheim

Analysis: Afatinib, the active ingredient of Gilotrif®, is a tyrosine kinase inhibitor. It binds to the kinase domains of EGFR (Erb B1), HER2 (Erb B2), and HER4 (Erb B4), and irreversibly inhibits tyrosine kinase auto-phosphorylation, resulting in downregulation of Erb B signaling.

A multicenter, randomized, open-label study (Study 1) was performed to assess the safety and efficacy of Gilotrif® when used as first-line treatment of adults (N=345) with EGFR mutation-positive, metastatic NSCLC. Patients were randomized to Gilotrif® 40mg daily (N=230) or up to 6 cycles of pemetrexed/cisplatin (chemotherapy; N=115). The main efficacy outcome was progression-free survival (PFS), while other outcomes assessed included the objective response rate (ORR) and overall survival (OS). Results suggested that there was a statistically significant improvement in PFS for patients in the Gilotrif® group as compared with the chemotherapy group. The median PFS was 11.1 months with Gilotrif® treatment as compared with 6.9 months with chemotherapy ($p<0.001$). There were 152 deaths/progressions in the Gilotrif® group (66.1%) as compared with 69 in the chemotherapy group (60%). The OS was not statistically significantly different between treatments, with the median OS being 28.1 months with Gilotrif® vs 28.2 months with chemotherapy ($p=0.55$). There was not a statistically significant difference in the number of deaths between treatments (116 [50.4%] vs 59 [51.2%], respectively). The ORR was higher with Gilotrif® as compared with chemotherapy (50.4% vs 19.1%), and the median response duration was 12.5 months vs 6.7 months, respectively.

A 2013 phase II single-arm trial by Katakami et al[2] included 62 Japanese adults with NSCLC (pulmonary adenocarcinoma) who progressed after ≥12 weeks of prior erlotinib and/or gefitinib treatment to assess the

objective response rate (ORR; primary outcome) of these adults now receiving afatinib 50mg daily. 82.3% (N=51) met criteria of acquired resistance to erlotinib and/or gefitinib. Results suggested that 8.2% (N=5) had a confirmed ORR (partial response). The median progression free survival (PFS) was 4.4 months, and the median overall survival (OS) was 19 months.

Miller et al[3] conducted a 2012 phase 3, randomized, placebo-controlled trial assessing the effects of afatinib vs placebo on OS in a group of adults (N=585) with adenocarcinoma who had received 1-2 previous chemotherapy regimens and had disease progression after ≥12 weeks of treatment with erlotinib or gefitinib. Results suggested that the median OS was 10.8 months in the afatinib group vs 12 months in the placebo group, which was numerically lower but not statistically significantly different (p=0.74). Nevertheless, median PFS was significantly longer in the afatinib group (3.3 months) vs placebo (1.1 months; p<0.0001). The authors concluded that in this population who failed at least 12 weeks of previous EGRR tyrosine-kinase inhibitor treatment, afatinib did not provide additional benefit in OS as compared with placebo, but there was benefit in PFS.

There were no head-to-head, active comparator trials comparing afatinib with other tyrosine kinase inhibitors with the same indication; however, there was some evidence seen that afatinib may be beneficial to increase PFS in a population who had disease progression after ≥12 weeks of prior erlotinib and/or gefitinib treatment. There is no evidence at this time to support that Gilotrif® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Gilotrif® be added to the Recommended List as a non-recommended drug.

PDL Placement:

- ☐ **Recommended**
- ☒ **Non-Recommended**
- ☐ **Preferred with Conditions**

References

[1] Gilotrif [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2013.

[2] Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: A phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol*. 2013; 31(27): 3335-41.

[3] Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomized trial. *Lancet Oncol*. 2012; 13(5): 528-38.