Afanix final Insert

COMPOSITION

Afanix 20 Tablet: Each film coated tablet contains Afatinib Dimaleate INN equivalent to Afatinib 20 mg.

Afanix 40 Tablet: Each film coated tablet contains Afatinib Dimaleate INN equivalent to Afatinib 40 mg.

CLINICAL PHARMACOLOGY

Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation
of ErbB signaling.
Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon
21 L858R mutations, including some with a secondary T790M mutation, at Afatinib concentrations achieved, at least transiently, in patients. In addition, Afatinib inhibited in vitro proliferation of cell lines overexpressing HER2.
Treatment with Afatinib resulted in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of Afatinib (50 mg once daily) on the QTc interval was evaluated in an open-label, single-arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected.

Pharmacokinetics

Absorption and Distribution

Following oral administration of Afatinib tablets, time to peak Afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Maximum concentration (C_{max}) and area under the concentration-time curve
from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg Afatinib tablets was 92% as compared to an oral solution. In vitro binding of Afatinib to human plasma proteins is approximately 95%.
A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition.

Metabolism and Elimination

Covalent adducts to proteins are the major circulating metabolites of Afatinib and enzymatic metabolism of Afatinib is minimal.
In humans, excretion of Afatinib is primarily via the feces (85%) with 4% recovered in the urine following a single oral dose of [14C]-labeled Afatinib solution. The parent compound accounted for 88% of the recovered dose.
The elimination half-life of Afatinib is 37 hours after repeat dosing in cancer patients. Steady-state
plasma concentrations are achieved within 8 days of repeat dosing of Afatinib resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max}.

Specific populations

Renal Impairment: The median trough Afatinib plasma concentrations in patients with mild (CLcr 60-89 mL/min) and moderate (CLcr 30-59 mL/min) renal impairment were 27% and 85% higher than those in patients with normal renal function (CLcr>_90 mL/min). Afatinib has not been
studied in patients with severely impaired renal function (CLcr <30 mL/min).

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the Afatinib exposure following a single dose of Afatinib. Subjects with severe (Child Pugh C) hepatic dysfunction have
not been studied.

Body Weight, Gender, Age, and Race: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of Afatinib.

Drug Interactions

Effect of P-gp Inhibitors and Inducers on Afatinib: The effect of ritonavir dosing time relative to a single oral dose of Afatinib was evaluated in healthy subjects taking 40 mg of Afatinib alone as compared to those after ritonavir (200 mg twice daily for 3 days) co-administration at 6 hours after Afatinib administration. The relative bioavailability for AUC0-∞ and Cmax of afatinib was 119% and 104% when co-administered with ritonavir, and 111% and 105% when ritonavir was administered 6 hours after taking Afatinib. In another study, when ritonavir (200 mg twice daily for 3 days) was administered 1 hour before a 20 mg single dose of Afatinib, exposure to afatinib increased by 48% for AUC0-∞ and 39% for Cmax.
Pre-treatment with a potent inducer of P-gp, rifampicin (600 mg once daily for 7 days) decreased
the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}).

P-glycoprotein (P-gp): Based on *in vitro* data, afatinib is a substrate and an inhibitor of P-gp.

Breast Cancer Resistance Protein (BCRP): Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

Effect of CYP450 Enzyme Inducers and Inhibitors on Afatinib: *In vitro* data indicated that drug-drug interactions with Afatinib due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely. The metabolites formed by CYP450-dependent reactions

were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. In humans, enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Effect of Afatinib on CYP450 Enzymes: Afatinib is not an inhibitor or an inducer of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4) in cultured primary human hepatocytes. Therefore, afatinib is unlikely to affect the metabolism of other drugs that are substrates of CYP450 enzymes.

INDICATIONS

Afatinib is indicated 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.
Limitation of Use: Safety and efficacy of Afatinib have not been established in patients whose tumors have other EGFR mutations.

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dose of Afatinib is 40 mg orally once daily until disease progression or no longer tolerated by the patient. Afatinib should be taken at least 1 hour before or 2 hours after a meal. Patient should not take a missed dose within 12 hours of the next dose.

Dosage Modification

Withhold Afatinib for any drug-related adverse reactions of:
• NCI CTCAE* Grade 3 or higher
• Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication
• Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable
• Renal dysfunction of Grade 2 or higher
Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstitute Afatinib at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.
Permanently discontinue Afatinib for:
• Life-threatening bullous, blistering, or exfoliative skin lesions
• Confirmed interstitial lung disease (ILD)

• Severe drug-induced hepatic impairment
• Persistent ulcerative keratitis
• Symptomatic left ventricular dysfunction
• Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

P-gp Inhibitors

For patients who require therapy with a P-glycoprotein (P-gp) inhibitor, reduce Afatinib daily dose

by 10 mg if not tolerated. Resume the previous dose after discontinuation of the P-gp inhibitor as
tolerated.

P-gp Inducers

For patients who require chronic therapy with a P-gp inducer, increase Afatinib daily dose by 10 mg as tolerated. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D

Risk Summary
Based on its mechanism of action, Afatinib can cause fetal harm when administered to a pregnant
woman. Afatinib was embryotoxic and, in animals with maternal toxicity, led to abortions at late gestational stages in rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers
It is not known whether Afatinib is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 times higher than those found in plasma from 1 to 6 hours
after administration. Because many drugs are present in human milk and because of the potential
for serious adverse reactions in nursing infants from Afatinib, a decision should be made whether
to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
the mother.

Pediatric Use
Safety and effectiveness of Afatinib in pediatric patients have not been established.

Geriatric Use
Of the 3865 patients in the clinical studies of Afatinib, 32% of patients were 65 years and older, while 7% were 75 years and older. No overall differences in safety were observed between patients 65 years and over and younger patients. 39% of the 345 patients were 65 years of age or older and 4% were 75 years or older. No overall differences in effectiveness were observed between patients 65 years and older and younger patients.

Females and Males of Reproductive Potential
Contraception
Females
Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with Afatinib, and for at least 2

weeks after the last dose of Afatinib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking Afatinib.

Renal Impairment
Afatinib has not been studied in patients with severely impaired renal function (Creatinine clearance [CLcr] <30 mL/min). Adjustments to the starting dose of Afatinib are not considered necessary in patients with mild (CLcr 60-89 mL/min) renal impairment. Closely monitor patients with moderate (CLcr 30-59 mL/min) to severe (CLcr <30 mL/min) renal impairment and adjust Afatinib dose if not tolerated.

Hepatic Impairment
Afatinib has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of Afatinib are not considered necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust Afatinib dose if not tolerated.

OVERDOSAGE
Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of Afatinib (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase (<1.5 times upper limit of normal [ULN]). Both subjects recovered.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea may result in dehydration and renal failure. Withhold Afatinib for severe and prolonged diarrhea not responsive to antidiarrheal agents.
Bullous and Exfoliative Skin Disorders: Severe bullous, blistering, and exfoliating lesions occurred in 0.15% of patients. Discontinue for life-threatening cutaneous reactions. Withhold Afatinib for severe and prolonged cutaneous reactions.
Interstitial lung disease (ILD): Occurs in 1.5% of patients. Withhold Afatinib for acute onset or worsening of pulmonary symptoms. Discontinue Afatinib if ILD is diagnosed.
Hepatic toxicity: Fatal hepatic impairment occurs in 0.18% of patients. Monitor with periodic liver testing. Withhold or discontinue Afatinib for severe or worsening liver tests.
Keratitis: Occurs in 0.8% of patients. Withhold Afatinib for keratitis evaluation. Withhold or discontinue Afatinib for confirmed ulcerative keratitis.
Embryofetal toxicity: Can cause fetal harm. Advise females of the potential hazard to the fetus and to use highly effective contraception.

ADVERSE EFFECT
Most common adverse reactions (>_20%) are diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, pruritus.

DRUG INTERACTION
Effect of P-glycoprotein (P-gp) Inhibitors and Inducers
Oral administration of a P-gp inhibitor (Ritonavir at 200 mg twice daily) 1 hour before administration of Afatinib increased systemic exposure to Afatinib by 48%. There was no change
in Afatinib exposure when Ritonavir was administered simultaneously with or 6 hours after

Afatinib. Concomitant taking of P-gp inhibitors (including but not limited to Ritonavir, Cyclosporine
A, Ketoconazole, Itraconazole, Erythromycin, Verapamil, Quinidine, Tacrolimus, Nelfinavir, Saquinavir, and Amiodarone) with Afatinib can increase exposure to Afatinib.
Co-administration with oral dose of a P-gp inducer (Rifampicin at 600 mg once daily for 7 days) decreased exposure to Afatinib by 34%. Concomitant taking of P-gp inducers (including but not limited to Rifampicin, Carbamazepine, Phenytoin, Phenobarbital, and St. John's wort) with Afatinib can decrease exposure to Afatinib.

PHARMACEUTICAL INFORMATION

Storage Conditinons
Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Afanix 20 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

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