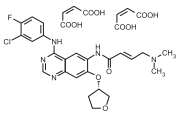
AFATIZ 20/30/40
Afatinib Tablets 20mg/30mg/40mg

Rx only
COMPOSITION

AFATIZ 20
Afatinib Tablets 20 mg
Afatinib dimaleate equivalent to Afatinib 20mg
Excipients q.s.
Colours: Titanium dioxide

AFATIZ 30
Afatinib Tablets 30 mg
Afatinib dimaleate equivalent to Afatinib 30mg
Excipients q.s.
Colours: Titanium dioxide

AFATIZ 40
Afatinib Tablets 40 mg
Afatinib dimaleate equivalent to Afatinib 40mg
Excipients q.s.
Colours: Titanium dioxide



DESCRIPTION

Afatinib tablets contain , a tyrosine kinase inhibitor which is a 4-anilinoquinazoline. Afatinib is presented as the dimaleate salt, with the chemical name 2-butenamide, N-[4-[(3-chloro-4-fluorophenyl amino]-7-[[(3S)-tetrahydro-3-furanyl] oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2E)-, (2Z)-2-butenedioate (1:2). Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of $C_{32}H_{33}ClFN_5O_{11}$, and a molecular weight of 718.1 g/mol. Afatinib tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively). The inactive ingredients of Afatinib are the following: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and Coating: Titanium dioxide.

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 auto phosphorylation, resulting in downregulation of ErbB signaling. Certain mutations in EGFR, including non-resistant mutations in its kinase domain, can result in increased auto phosphorylation of the receptor, leading to receptor activation, sometimes in the absence of ligand binding, and can support cell proliferation in NSCLC. Non-resistant mutations are defined as those occurring in exons constituting the kinase domain of EGFR that lead to increased receptor activation and where efficacy is predicted by 1) clinically meaningful tumor shrinkage with the recommended dose of Afatinib and/or 2) inhibition of cellular proliferation or EGFR tyrosine kinase phosphorylation at concentrations of Afatinib sustainable at the recommended dosage according to validated methods. The most commonly found of these mutations are exon 21 L858R substitutions and exon 19 deletions. Afatinib demonstrated inhibition of auto phosphorylation and/or in vitro proliferation of cell lines expressing wild-type EGFR and in those expressing selected EGFR exon 19 deletion mutations, exon 21 L858R mutations, or other less common non-resistant mutations, at Afatinib concentrations achieved 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: 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 in the study.

Pharmacokinetics:

Absorption: 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 (AUC0-INF) 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. 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}.

Distribution: In vitro binding of Afatinib to human plasma proteins is approximately 95%.

Elimination: The elimination half-life of Afatinib is 37 hours after repeat dosing in cancer patients.

Metabolism: Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of Afatinib is minimal. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. Approximately 2% of the Afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Excretion: In humans, excretion of Afatinib is primarily via the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose.

INDICATIONS AND USAGE

EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer

Afatinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

Limitations of Use: The safety and efficacy of Afatinib have not been established in patients whose tumors have resistant EGFR mutations.

Previously Treated, Metastatic Squamous NSCLC

AFATINIB is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

DOSAGE AND ADMINISTRATION

The recommended dosage of Afatinib is 40 mg orally once daily until disease progression or no longer tolerated by the patient.

Take Afatinib at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Diarrhea
- Bullous and Exfoliative Skin Disorders
- Interstitial Lung Disease
- Hepatic Toxicity
- Gastrointestinal Perforation
- Keratitis

EGFR Mutation-Positive Metastatic NSCLC

Serious adverse reactions were reported in 29% of patients treated with Afatinib. The most frequent serious adverse reactions reported in patients treated with Afatinib were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in Afatinib -treated patients in LUX-Lung 3 included pulmonary toxicity/ILD -like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of Afatinib -treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with Afatinib were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%). Discontinuation of therapy in Afatinib -treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in Afatinib -treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Table 1 Adverse Reactions Reported in ≥10% of Afatinib -Treated Patients in LUX-Lung 3*

Adverse Reaction	Afatinib n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3† (%)	All Grades (%)	Grade 3† (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis1	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/acneiform	90	16	11	0
dermatitis2				
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia3	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

A/s. 182 x 100 mm Black

Previously Treated, Metastatic Squamous NSCLC

Serious adverse reactions occurred in 44% of patients treated with Afatinib. The most frequent serious adverse reactions in patients treated with Afatinib were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in Afatinib -treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

The most frequent adverse reactions that led to discontinuation in Afatinib -treated patients were diarrhea (4.1%) and rash/acne (2.6%).

Adverse Reaction	Afatinib n = 392		Erlotinib n = 395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis[1]	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	70	7	70	11
Pruritus	10	0	13	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2
Infections				
Paronychia[3]	11	1	5	0

*NCI CTCAE v 3.0

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

[3]Includes paronychia, nail infection, nail bed infection

Less Common Adverse Reactions

Other adverse reactions reported in patients treated with Afatinib in LUX-Lung 3 and LUX-Lung 8 include:

Skin and subcutaneous disorders: nail disorders occurred in 9.2% and 2.8% of patients, respectively.

CONTRAINDICATIONS

None.

DRUG INTERACTIONS: 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 can increase Afatinib exposure to afatinib. Reduce Afatinib daily dose as recommended.

Concomitant taking of P-gp inducers Afatinib can decrease exposure to Afatinib Increase daily dose Afatinib as recommended.

WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours.

Bullous and Exfoliative Skin Disorders: Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating skin lesions, occurred. Discontinue Afatinib in patients who develop life-threatening bullous, blistering, or exfoliating skin lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2 cutaneous reactions, or Grade 3 cutaneous reactions, withhold Afatinib until the adverse reaction resolves to Grade 1 or less and resume Afatinib with appropriate dose reduction

Interstitial Lung Disease: Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred. Withhold Afatinib during evaluation of patients with suspected ILD and discontinue in Afatinib patients with confirmed ILD.

Hepatic Toxicity: Liver test abnormalities of any grade occurred in 17.5% of the patients treated with, Afatinib of which 3.5% had Grade 3-4 liver test abnormalities. In LUX-Lung 8, liver test abnormalities of any grade occurred in 6% of the patients treated with Afatinib, of which 0.2% had Grade 3-4 liver test abnormalities. In patients who develop severe hepatic impairment while taking Afatinib, discontinue treatment.

Gastrointestinal Perforation: Gastrointestinal perforation, including fatal cases, has occurred with Afatinib. Patients receiving concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-angiogenic agents, or patients with increasing age or who have an underlying history of gastrointestinal ulceration, underlying diverticular disease or bowel metastases may be at increased risk of perforation. Permanently discontinue Afatinib in patients who develop gastrointestinal perforation

Keratitis: Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, Afatinib can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryo toxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of Afatinib.

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.

HOW SUPPLIED

Afatinib Tablets 20/30/40 mg supplied in a bottle of 28 tablets packed in a HDPE container

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59 to 86°F).

SHELF LIFE

24 months

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited
Factory: Tukucha, Nala-1,
Banepa, Nepal.
Regd. Office: Maligoan-5,
Kathmandu, Nepal.