Anib- 40

Afatinib Dimaleate INN 40 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Afatinib 40 mg as Afatinib Dimaleate INN.

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.

Pharmacokinetics:

Absorption and Distribution: Following oral administration of Anib tablets, time to peak Afatinib plasma concentrations (Tmax) is 2 to 5 hours. Maximum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg Anib 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 Cmax by 50% and AUC0-∞ 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 Anib resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for Cmax.

Indications:

EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer: Anib 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: The safety and efficacy of Anib have not been established in patients whose tumors have other EGFR mutations.

Previously Treated, Metastatic Squamous NSCLC: Anib is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

Dosage and Administration:

Patient Selection for EGFR Mutation-Positive Metastatic NSCLC: Patients should be selected for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens.

Recommended Dose: The recommended dose of Anib is 40 mg orally, once daily until disease progression or no longer tolerated by the patient.

Severe Renal Impairment: The recommended dose of Anib in patients with severe renal impairment (estimated glomerular filtration rate [eGFR *] 15 to 29 mL/min /1.73 m²) is 30 mg orally, once daily.

Anib should be taken at least 1 hour before or 2 hours after a meal. A missed dose should not be taken within 12 hours of the next dose. Or, as directed by the registered physicians.

Dose Modifications for Adverse Reactions: Anib should be withheld for any 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 impairment of Grade 2 or higher

Side Effects:

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

Contraindications: It is contraindicated in patients with known hypersensitivity to Afatinib or any other components of this product.

Use in Pregnancy and Lactation: Anib can cause fetal harm when administered to a pregnant woman. There are no available data on the use of Anib in pregnant women.

Lactation: There are no data on the presence of Afatinib in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in nursing infants from Anib, a lactating woman should be advised not to breastfeed during treatment with Anib and for 2 weeks after the final dose.

Females and Males of Reproductive Potential: Females: Anib can cause fetal harm when administered to a pregnant woman. Females should be advised of reproductive potential to use effective contraception during treatment with Anib, and for at least 2 weeks after the last dose of Anib.

Infertility: Based on results from an animal fertility study, Anib may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible.

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

Drug Interactions:

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers: 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 Anib can increase exposure to Afatinib. Concomitant taking of P- gp inducers (including but not limited to Rifampicin, Carbamazepine, Phenytoin, Phenobarbital, and St. John's wort) with Anib can decrease exposure to Afatinib.

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 in 697 (16%) of the 4257 patients who received Anib across 44 clinical trials. In Study 1, diarrhea occurred in 96% of patients treated with Anib (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with Anib, of which 1.3% were Grade 3. For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, Anib should be withheld until diarrhea resolves to Grade 1 or less, and resume Anib with appropriate dose reduction.

Bullous and Exfoliative Skin Disorders: Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received Anib across clinical trials. In Study 1, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Anib should be discontinued in patients who develop life-threatening bullous, blistering, or exfoliating lesions.

Interstitial Lung Disease (ILD): Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received Anib across clinical trials; of these, 0.4% were fatal. Anib should be withheld during evaluation of patients with suspected ILD, and Anib should be discontinued in patients with confirmed ILD.

Hepatic Toxicity: In 4257 patients who received Anib across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with ANib, of which 3.5% had Grade 3-4 liver test abnormalities. Periodic liver testing should be obtained in patients during treatment with Anib. Anib should be withheld in patients who develop worsening of liver function. In patients who develop severe hepatic impairment while taking Anib, treatment should be discontinued.

Keratitis: Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with Anib among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in Study 1, with Grade 3 in 0.4%. Anib should be withheld during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with Anib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Anib should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Overdose: Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of Anib (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.

Storage: Store below 30°C in a cool and dry place, away from sunlight. Keep out of reach of children.

Packaging: Each box contains 30 tablets in a blister pack.