Eronib-150

Erlotinib HCl INN 150 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Erlotinib 150 mg as Erlotinib HCl INN.

Clinical Pharmacology: Erlotinib reversibly inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor and thereby inhibiting further downstream signaling. Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 (L858R) mutations is higher than its affinity for the wild type receptor.

Mechanism of Action: Epidermal growth factor receptor (EGFR) is expressed on the cell surface of both normal and cancer cells. In some tumor cells signaling through this receptor plays a role in tumor cell survival and proliferation irrespective of EGFR mutation status. Erlotinib reversibly inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor and thereby inhibiting further downstream signaling. Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 (L858R) mutations is higher than its affinity for the wild type receptor. Erlotinib inhibition of other tyrosine kinase receptors has not been fully characterized.

Pharmacokinetics:

Absorption: Erlotinib is about 60% absorbed after oral administration. Peak plasma levels occur 4 hours after dosing. Food increased the bioavailability of Erlotinib to approximately 100%.

Distribution: Erlotinib is 93% protein bound to plasma albumin and alpha-1 acid glycoprotein (AAG). It has an apparent volume of distribution of 232 liters.

Elimination: Erlotinib is eliminated with a median half-life of 36.2 hours in patients receiving the single-agent Eronib 2nd/3rd line regimen. Time to reach steady state plasma concentration would therefore be 7-8 days.

Metabolism: Erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1, in vitro.

Excretion: Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

Indications: Non-Small Cell Lung Cancer (NSCLC): It is indicated for the 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 receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.

Pancreatic Cancer: Erlotinib in combination with Gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Dosage and Administration: Recommended Dose – NSCLC: The recommended daily dose of Eronib for NSCLC is 150 mg taken on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Recommended Dose - Pancreatic Cancer: The recommended daily dose of Eronib for pancreatic cancer is 100 mg taken once daily in combination with Gemcitabine. Eronib should be taken on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Dose Modifications:

Adverse Reactions		
Pulmonary	Interstitial Lung Disease (ILD)	Discontinue Eronib
	During diagnostic evaluation for possible ILD	Withhold Eronib
Hepatic	Severe hepatic toxicity that does not improve significantly or resolve within three weeks	Discontinue Eronib
	In patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline	Withhold Eronib and consider discontinuation
	In patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal	Withhold Eronib and consider discontinuation
Renal	For severe (CTCAE grade 3 to 4) renal toxicity	Withhold Eronib and consider discontinuation
Gastrointestinal	Gastrointestinal perforation	Discontinue Eronib
	For persistent severe diarrhea not responsive to medical management (e.g., loperamide)	Withhold Eronib
Skin	Severe bullous, blistering or exfoliating skin conditions	Discontinue Eronib
	For severe rash not responsive to medical management	Withhold Eronib
Ocular	Corneal perforation or severe ulceration	Discontinue Eronib
	For keratitis of (NCI CTC version 4.0) grade 3-4 or for grade 2 lasting more than 2 weeks	Withhold Eronib
	For acute/worsening ocular disorders such as eye pain	Withhold Eronib and consider discontinuation

Drug Interactions		
CYP3A4 inhibitors	If severe reactions occur with concomitant use of strong CYP3A4 inhibitors [such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grap efruit or grapefruit juice] or when using concomitantly with an inhibitor of both CYP3A4 and CYP1A2 (e.g., ciprofloxacin)	Reduce Eronib by 50 mg decrements; avoid concomitant use if possible
CYP3A4 inducers	Concomitant use with CYP3A4 inducers, such as rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort	Increase Eronib by 50 mg increments at 2-week intervals to a maximum of 450 mg as tolerated. Avoid concomitant use if possible
Concurrent Cigarette Smoking	Concurrent cigarette smoking	Increase Eronib by 50 mg increments at 2-week intervals to a maximum of 300 mg. Immediately reduce the dose of Eronib to the recommended dose (150mg or 100mg daily) upon cessation of smoking
Proton Pump inhibitors	Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper GI tract for anextended period	Avoid concomitant use if possible
H_2-receptor antagonists	If treatment with an H_2-receptor antagonist such as ranitidine is required, separate dosing.	Eronib must be taken 10 hours after the H_2-receptor antagonist dosing and at least 2 hours before the next dose of the H_2-receptor antagonist
Antacids	The effect of antacids on Erlotinib pharmacokinetics has not been evaluated.	The antacid dose and the Eronib dose should be separated by several hours, if an antacid is necessary

Or, as directed by the registered physicians.

Side Effects: The most common side effects are- Interstitial Lung Disease (ILD), Renal Failure, Hepatotoxicity with or without Hepatic Impairment, Gastrointestinal Perforation, Bullous and Exfoliative Skin Disorders, Cerebrovascular Accident, Microangiopathic Hemolytic Anemia with Thrombocytopenia, Ocular Disorders, Hemorrhage in Patients taking Warfarin.

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

Use in pregnancy and lactation: Pregnancy category D. Eronib can cause fetal harm when administered to a pregnant woman. If it 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. **Lactation:** There is no information regarding the presence of Erlotinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Women should be advised not to breastfeed during treatment with Eronib and for 2 weeks after the final dose. **Females and Males of Reproductive Potential: Contraception: Females:** Eronib can cause fetal harm when administered to a pregnant woman.Females of reproductive potential should be advised to use effective contraception during treatment with Eronib and for one month after the last dose of it.

Patients should be counseled on pregnancy planning and prevention.

- Females of reproductive potential should be advised to use highly effective contraception during treatment with Eronib, and for at least 2 weeks after the last dose of Eronib.
- Patients should be advised to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with Eronib.
- Breast-feeding mothers should be advised to discontinue nursing while receiving Eronib. Patients should be advised to stop smoking and the dose of Eronib may need to be adjusted if they smoke.

Pediatric Use: The safety and effectiveness of Eronib in pediatric patients have not been established. **Hepatic Impairment:** Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with Eronib treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. Patients with hepatic impairment should be monitored (total bilirubin greater than upper limit of normal (ULN) or Child-Pugh A, B and C) during therapy with Eronib. Treatment with Eronib should be used with increased monitoring in patients with total bilirubin greater than 3 x ULN.

Drug Interactions: CYP3A4 Inhibitors: Co-administration of Eronib with a strong CYP3A4 inhibitor or a combined CYP3A4 and CYP1A2 inhibitor increased Erlotinib exposure. Co-administering Eronib should be avoided with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit or grapefruit juice) or a combined CYP3A4 and CYP1A2 inhibitor (e.g., ciprofloxacin). **CYP3A4 Inducers:** Pre-treatment with a CYP3A4 inducer prior to Eronib decreased Erlotinib exposure. Eronib dosage should be increased if co-administration with CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, rifabutin, rifapentine, phenobarbital and St. John's wort) is unavoidable. **Drugs that increase Gastric pH :** Co-administration of Eronib with proton pump inhibitors (e.g., omeprazole) and H2 receptor antagonists (e.g., ranitidine) decreased Erlotinib exposure. For proton pump inhibitors, concomitant use should be avoided if possible. For H2 receptor antagonists and antacids, dosing schedule should be modified. The dose of Eronib should be increased when co-administered with gastric pH elevating agents is not likely to compensate for the loss of exposure. **Anticoagulants:** Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International Normalized Ratio (INR) and bleeding adverse reactions, which in some cases were fatal, have been reported in patients receiving Eronib. Prothrombin time or INR should be regularly monitored in patients taking coumarin-derived anticoagulants. Dose modifications of Eronib are not recommended.

Precautions: Interstitial Lung Disease (ILD): Cases of serious ILD, including fatal cases, can occur with Eronib treatment. The overall incidence of ILD in approximately 32,000 Eronib-treated patients in uncontrolled studies and studies with concurrent chemotherapy was approximately 1.1%. In patients with ILD, the onset of symptoms was between 5 days to more than 9 months (median 39 days) after initiating Eronib therapy. Eronib should be withheldfor acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation. If ILD is confirmed, Eronib should be permanently discontinued. **Renal Failure:** Hepatorenal syndrome, severe acute renal failure including fatal cases, and renal insufficiency can occur with Eronib treatment. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. The pooled incidence of severe renal impairment in the 3 monotherapy lung cancer studies was 0.5% in the Eronib arms and 0.8% in the control arms. The incidence of renal impairment in the pancreatic cancer study was 1.4% in the Eronib plus Gemcitabine arm and 0.4% in the control arm. Eronib should be withheld in patients developing severe renal impairment until renal toxicity is resolved. Periodic monitoring of renal function and serum electrolytes should be performed during Eronib treatment. **Hepatotoxicity with or without Hepatic Impairment:** Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with Eronib treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. In clinical studies where patients with moderate to severe hepatic impairment were excluded, the pooled incidence of hepatic failure in the 3 monotherapy lung cancer studies was 0.4% in the Eronib arms and 0% in the control arms. The incidence of hepatic failure in the pancreatic cancer study was 0.4% in the Eronib plus Gemcitabine arm and 0.4% in the control arm. In a pharmacokinetic study in 15 patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of these 15 patients died within 30 days of the last Eronib dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN. Periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) should be performed during treatment with Eronib. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Eronib should be withheld in patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal. Eronib should be withheld in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. It should be discontinued in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks. **Gastrointestinal Perforation:** Gastrointestinal perforation, including fatal cases, can occur with Eronib treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. The incidence of gastrointestinal perforation in the pancreatic cancer study was 0.4% in the Eronib plus Gemcitabine arm and 0% in the control arm. Eronib should be discontinued permanently in patients who develop gastrointestinal perforation. **Bullous and Exfoliative Skin Disorders:** Bullous, blistering and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal, can occur with Eronib treatment. The incidence of bullous and exfoliative skin disorders in the pancreatic cancer study was 0.4% in the Eronib plus Gemcitabine arm and 0% in the control arm. Eronib treatment should be discontinued if the patient develops severe bullous, blistering or exfoliating conditions. **Cerebrovascular Accident:** In the pancreatic carcinoma trial, seven patients in the Eronib/Gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/Gemcitabine group there were no cerebrovascular accidents. **Microangiopathic Hemolytic Anemia with Thrombocytopenia:** The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the 3 monotherapy lung cancer studies was 0% in the Eronib arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the Eronib plus Gemcitabine arm and 0% in the control arm. **Ocular Disorders:** Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can occur with Eronib treatment and can lead to corneal perforation or ulceration. Eronib therapy should be interrupted or discontinued if patients present with acute or worsening ocular disorders such as eye pain. **Hemorrhage in Patients taking Warfarin:** Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when Eronib and Warfarin are administered concurrently. Prothrombin time and INR during Eronib treatment in patients should be regularly monitored taking Warfarin or other coumarin-derivative anticoagulants.

Overdose: Eronib should be withheld in patients with an overdose or suspected overdose and symptomatic treatment should be instituted.

Storage: Store at 25°C in a cool and dry place, away from sunlight. Keep out of the reach of children.

Packing: Each box contains 2x14's tablets in Alu- Alu blister pack.