Hertinib

Neratinib INN 40 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each tablet contains Neratinib 40 mg as Neratinib Maleate INN.

Mechanism of Action: Neratinib is a kinase inhibitor that irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4. In vitro, Neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines. Neratinib human metabolites M3, M6, M7 and M11 inhibited the activity of EGFR, HER2 and HER4 in vitro. In vivo, oral administration of Neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR.

Pharmacokinetics:

Absorption: The Neratinib and major active metabolites M3, M6 and M7 peak concentrations are reached in the range of 2 to 8 hours after oral administration.

Distribution: In patients, following multiple doses of Hertinib, the mean (%CV) apparent volume of distribution at steady-state (Vss/F) was 6433 (19%) L. In vitro protein binding of Neratinib in human plasma was greater than 99% and independent of concentration. Neratinib bound predominantly to human serum albumin and human alpha-1 acid glycoprotein.

Elimination: Following 7 days of daily 240 mg oral doses of Hertinib in healthy subjects, the mean (%CV) plasma halflife of Neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (77%), 13.8 (50%) and 10.4 (33%) hours, respectively. The mean elimination half-life of Neratinib ranged from 7 to 17 hours following a single oral dose in patients. Following multiple doses of Hertinib at once-daily 240 mg in cancer patients, the mean (%CV) CL/F after first dose and at steady state (day 21) were 216 (34%) and 281 (40%) L/hour, respectively.

Metabolism: Neratinib is metabolized primarily in the liver by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

Excretion: After oral administration of 200 mg (0.83 times of approved recommended dosage) radiolabeled neratinib oral formulation, fecal excretion accounted for approximately 97.1% and urinary excretion accounted for 1.13% of the total dose. Sixty-one percent of the excreted radioactivity was recovered within 96 hours and 98% was recovered after 10 days.

Indications:

Extended Adjuvant Treatment of Early-Stage Breast Cancer: Hertinib as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER_2)- positive breast cancer, to follow adjuvant Trastuzumab based therapy.

Advanced or Metastatic Breast Cancer: Hertinib in combination with Capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER_2-positive breast cancer who have received two or more prior anti-HER_2 based regimens in the metastatic setting.

Dosage and Administration:

Antidiarrheal Prophylaxis: Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of Hertinib. Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. Hertinib dose interruptions and dose reductions may also be required to manage diarrhea.

The recommended dose of Hertinib is 240 mg (six tablets) given orally once daily with food, continuously for one year. Patients should be instructed to take Hertinib at approximately the same time every day. Hertinib tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing). If a patient misses a dose, missed dose should not be replaced, and patients should be instructed to resume Hertinib with the next scheduled daily dose. Or, as directed by the registered physicians.

Dose Modifications: For Adverse Reactions: Hertinib dose modification is recommended based on individual safety and tolerability. Hertinib should be discontinued for patients who fail to recover to Grade 0-1 from treatment-related toxicity, for toxicities that result in a treatment delay > 3 weeks, or for patients that are unable to tolerate 120 mg daily. Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent Grade 2 adverse reactions, etc.).

Dose Level	Hertinib Dose
Recommended starting dose	240 mg daily
First dose reduction	200 mg daily
Second dose reduction	160 mg daily
Third dose reduction	120 mg daily

Hertinib Dose Modifications and Management- General Toxicities

Severity of Toxicity	Action
Grade 3	Hold Hertinib until recovery to Grade ≤1 or baseline within 3 weeks of stopping treatment. Then resume Hertinib at the next lower dose level.
Grade 4	Discontinue Hertinib permanently.

Side Effects:

• Diarrhea • Hepatotoxicity

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

Use in Pregnancy and Lactation: Hertinib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Pregnant women should be advised of the potential risk to a fetus.

Lactation: No data are available regarding the presence of Neratinib or its metabolites in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Hertinib, lactating women should be advised not to breastfeed while taking Hertinib and for at least 1 month after the last dose.

Females and Males of Reproductive Potential:

Pregnancy: Hertinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with Hertinib. **Females:** Females of reproductive potential should be advised to use effective contraception during treatment with Hertinib and for at least 1 month after the last dose. **Males:** Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 3 months after the last dose of Hertinib.

Pediatric Use: The safety and efficacy of Hertinib in pediatric patients has not been established.

Geriatric Use: The incidence of serious adverse reactions in the Hertinib arm vs. placebo arm was 7.0% vs. 5.7% (< 65 years-old) and 9.9% vs. 8.1% (≥ 65 years-old). The serious adverse reactions most frequently reported in the ≥ 65 years-old group were vomiting (2.3%), diarrhea (1.7%), renal failure (1.7%), and dehydration (1.2%).

Hepatic Impairment: No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). Patients with severe, pre-existing hepatic impairment (Child Pugh Class C) experienced a reduction in Neratinib clearance and an increase in Cmax and AUC. Hertinib dosage should be reduced for patients with severe hepatic impairment.

Drug Interactions: Effect of Other Drugs on Hertinib:

Drug Interactions that Affect Neratinib

Gastric Acid Reducing Agents		
Clinical Impact	Concomitant use of Hertinib with a proton pump inhibitor, H_2-receptor antagonist, or antacid may decrease Neratinib plasma concentration. Decreased Neratinib AUC may reduce Hertinib activity. Lansoprazole (PPI) resulted in a decrease of Ne ratinib Cmax by 71% and AUC by 65%.	
	• PPIs	Avoid concomitant use
Prevention or Managemen	• H_2- receptor antagonists	Take Hertinib at least 2 hours before the next dose of the H_2- receptor antagonist or 10 hours after the H_2 -receptor antagonist
	• Antacids	Separate Hertinib dosing by 3 hours after antacids
Strong and Moderate CYP3A4 Inhibitors		
Clinical Impact	• Concomitant use of Hertinib with a strong CYP3A4 inhibitor (Ketoconazole) increased Neratinib Cmax by 321% and AUC by 481% • Concomitant use of Hertinib with other strong or moderate CYP3A4 inhibitors may increase Neratinib concentrations. • Increased Neratinib concentrations may increase the risk of toxicity.	
Prevention or Management	Avoid concomitant use of Hertinib with strong or moderate CYP3A4 inhibitors.	
Examples	Strong CYP3A4 inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole. **Moderate CYP3A4 inhibitors:** aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil.	
Strong or Moderate CYP3A4 Inducers		
Clinical Impact	• Concomitant use of Hertinib with a strong CYP3A4 inducer (Rifampin) reduced Neratinib Cmax by 76% and AUC by 87%. • Concomitant use of Hertinib with other strong or moderate CYP3A4 inducers may decrease Hertinib concentrations. • Decreased Neratinib AUC may reduce Hertinib activity.	
Prevention or Management	Avoid concomitant use of Hertinib with strong or moderate CYP3A4 inducers.	
Examples	**Strong CYP3A4 inducers:** carbamazepine, enzalutamide, mitotane, ph **Moderate CYP3A4 inducers:** bosentan, efavirenz, etravirine, modafinil enytoin, rifampin, St. John's wort.	

Effect of Hertinib on Other Drugs:

P- Glycoprotein (P- gp) Substrates: Concomitant use of Hertinib with digoxin, a P- gp substrate, increased digoxin concentrations. Increased concentrations of digoxin may lead to increased risk of adverse reactions including cardiac toxicity. Refer to the digoxin prescribing information for dosage adjustment recommendations due to drug interactions. Hertinib may inhibit the transport of other P- gp substrates (e.g., Dabigatran, Fexofenadine).

Precautions:

Diarrhea: Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with Hertinib. Diarrhea was reported in 95% of Hertinib- treated patients in ExteNET, a randomized placebo controlled trial. In the Hertinib arm, Grade 3 diarrhea occurred in 40% and Grade 4 diarrhea occurred in 0.1% of patients. The majority of patients (93%) had diarrhea in the first month of treatment, the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1- 350), and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1- 139). Patients should be monitored for diarrhea and treated with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, fluid and electrolytes should be administered as needed, Hertinib should be interrupted, and subsequent doses should be reduced. Stool cultures should be performed as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, neutropenia).

Hepatotoxicity: Hertinib has been associated with hepatotoxicity characterized by increased liver enzymes. In ExteNET, 9.7% of patients experienced an alanine aminotransferase (ALT) increase ≥ 2 x ULN, 5.1% of patients experienced an aspartate aminotransferase (AST) increase ≥ 2 x ULN, and 1.7% of patients experienced an AST or ALT elevation > 5 x ULN (≥ Grade 3). Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 1.7% of Hertinib - treated patients. Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with Hertinib monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. These tests should also be performed in patients experiencing Grade 3 diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant tenderness, fever, rash, or eosinophilia.

Embryo- Fetal Toxicity: Hertinib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 1 month after the last dose.

Overdose: There is no specific antidote, and the benefit of hemodialysis in the treatment of Hertinib overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken.

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

Packing: Each container contains 30 tablets in a box.