Hernix

Neratinib

COMPOSITION :

Each flim coated tablet contains Neratinib Maleate INN equivalent to Neratinib 40 mg

CLINICAL PHARMACOLOGY

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

Neratinib exhibits a non-linear PK profile with less than dose proportional increase of AUC with the increasing daily dose over the range of 40 to 400 mg.

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.

Effect of Food
The food-effect assessment was conducted in healthy volunteers who received Neratinib 240 mg under fasting conditions and with high fat food (approximately 55% fat, 31% carbohydrate, and 14% protein) or standard breakfast (approximately 50% carbohydrate, 35% fat, and 15% protein). A high fat meal increased Neratinib C_{max} and AUC_{inf} by 1.7-fold (90% CI: 1.1- 2.7) and 2.2-fold (90% CI: 1.4- 3.5), respectively. A standard breakfast increased the C_{max} and AUC_{inf} by 1.2-fold (90% CI: 0.97- 1.42) and 1.1-fold (90% CI: 1.02- 1.24), respectively.

Distribution

In patients, following multiple doses of Neratinib, 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 Neratinib in healthy subjects, the mean (%CV) plasma half-life 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 Neratinib 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).After oral administration of Neratinib, Neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of Neratinib in a healthy subject study (n=25), the systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11were 15%, 33%, 22% and 4% of the systemic Neratinib exposure (AUC) respectively.

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.

Specific Populations

Age, gender, race and renal function do not have a clinically significant effect on Neratinib pharmacokinetics

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Patients with Hepatic Impairment

Neratinib is mainly metabolized in the liver. Single doses of 120 mg Neratinib were evaluated in non-cancer patients with chronic hepatic impairment (n=6 each in Child Pugh Class A, B, and C) and in healthy subjects (n=9) with normal hepatic function. Neratinib exposures in the patients with Child Pugh Class A (mild impairment) and Child Pugh Class B (moderate impairment) were similar to that in normal healthy volunteers. Patients with severe hepatic impairment (Child Pugh Class C) had Neratinib C_{max} and AUC increased by 273% and 281%, respectively, as compared to the normal hepatic function controls.

Drug Interaction Studies

Gastric Acid Reducing Agents: In a trial of 15 healthy subjects, administration of a single 240 mg dose of Neratinib combined with a 30 mg lansoprazole dose at steady state decreased Neratinib C_{max} and AUC by 71% and 65%, respectively .

Strong and Moderate CYP3A4 Inhibitors: Concomitant use of ketoconazole (400 mg once-daily for 5 days), a strong inhibitor of CYP3A4, with a single oral 240 mg Neratinib dose in healthy subjects (n=24) increased Neratinib C_{max} by 321% and AUC by 481%.

The effect of moderate CYP3A4 inhibition has not been studied. Given Neratinib is predominantly metabolized by the CYP3A4 pathway and had a significant exposure change with strong CYP3A4 inhibition, the potential impact on Neratinib safety from concomitant use with moderate CYP3A4 inhibitors warrants consideration.

Strong and Moderate CYP3A4 Inducers:

Concomitant use of rifampin, a strong inducer of CYP3A4, with a single oral 240 mg Neratinib dose in healthy subjects (n=24) reduced Neratinib C_{max} by 76% and AUC by 87%. The AUC of active metabolites M6 and M7 were also reduced by 37-49% when compared to Neratinib administered alone.

The effect of moderate CYP3A4 induction has not been studied. Given Neratinib is predominantly metabolized by the CYP3A4 pathway and had a significant exposure change with strong CYP3A4 induction, the potential impact on Neratinib efficacy from concomitant use with moderate CYP3A4 inducers warrants consideration.

Effect of Neratinib on P-gp Transporters: Concomitant use of digoxin (a single 0.5 mg oral dose), a P-gp substrate, with multiple oral doses of Neratinib 240 mg in healthy subjects (n=18) increased the mean digoxin C_{max} by 54% and AUC by 32%

INDICATION

Neratinib is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy.

DOSAGE & 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 Neratinib.

Instruct patients to take Loperamide as directed in Table 1, titrating to 1-2 bowel movements per day.

Table 1: Loperamide Prophylaxis

Time on Neratinib	Dose	Frequency
Weeks 1-2 (days 1 - 14)	4 mg	Three times daily
Weeks 3-8 (days 15 - 56)	4 mg	Twice daily
Weeks 9-52 (days 57 – 365)	4 mg	As needed (not to exceed

Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. Neratinib dose interruptions and dose reductions may also be required to manage diarrhea.

Recommended Dose and Schedule

The recommended dose of Neratinib is 240 mg (six tablets) given orally once daily with food, continuously for one year. Instruct patients to take Neratinib at approximately the same time every day. Neratinib tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing). If a patient misses a dose, do not replace missed dose, and instruct the patient to resume Neratinib with the next scheduled daily dose.

DOSE MODIFICATIONS

Dose Modifications for Adverse Reactions

Neratinib dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Table 2 to Table 5. Discontinue Neratinib 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.).

Table 2: Neratinib Dose Modifications for Adverse Reactions

Dose Level	Neratinib 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

Table 3: Neratinib Dose Modifications and Management – General Toxicities

Severity of Toxicity[2]	Action

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

1 Refer to Table 4 and Table 5 below for management of diarrhea and hepatotoxicity

2 Per CTCAE v4.0

Dose Modifications for Diarrhea

Diarrhea management requires the correct use of antidiarrheal medication, dietary changes, and appropriate dose modifications of Neratinib. Guidelines for adjusting doses of Neratinib in the setting of diarrhea are shown in Table 4.

Table 4: Dose Modifications for Diarrhea

Severity of Diarrhea1	**Action**
• Grade 1 diarrhea [increase of < 4 stools per day over baseline] • Grade 2 diarrhea [increase of 4-6 stools per day over baseline] lasting < 5 days • Grade 3 diarrhea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting < 2 days	• Adjust antidiarrheal treatment • Diet modifications • Fluid intake of ~2L should be maintained to avoid dehydration • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent Neratinib administration.
• Any grade with complicated features2 • Grade 2 diarrhea lasting five days or longer3 • Grade 3 diarrhea lasting longer than 2 days3	• Interrupt Neratinib treatment • Diet modifications • Fluid intake of ~2L should be maintained to avoid dehydration • If diarrhea resolves to Grade 0-1 in one week or less, then resume Neratinib treatment at the same dose. • If diarrhea resolves to Grade 0-1 in longer than one week, then resume Neratinib treatment at reduced dose (see Table 2). • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent Neratinib administration.
• Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	• Permanently discontinue Neratinib treatment

• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue Neratinib treatment

Dose Modifications for Hepatic Impairment

Reduce the Neratinib starting dose to 80 mg in patients with severe hepatic impairment (Child Pugh C). No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B).

Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of Neratinib in the event of liver toxicity are shown in Table 5. Patients who experience ≥ Grade 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation.

Table 5: Dose Modifications for Hepatotoxicity

Severity of Hepatoxicity1	**Action**
• Grade 3 ALT (>5-20x ULN) OR • Grade 3 bilirubin (>3-10x ULN)	• Hold Neratinib until recovery to ≤ Grade 1 • Evaluate alternative causes • Resume Neratinib at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue Neratinib
• Grade 4 ALT (>20x ULN) OR • Grade 4 bilirubin (>10x ULN)	• Permanently discontinue Neratinib • Evaluate alternative causes

1 Per CTCAE v4.0

Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with Neratinib.
H2-receptor antagonists: Avoid concomitant use with Neratinib
Antacids: Separate dosing of Neratinib by 3 hours after antacids

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USE IN SPECIFIC POPULATION

Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, Neratinib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Neratinib to pregnant rabbits during organogenesis resulted in abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal exposures (AUC) approximately 0.2 times exposures in patients at the recommended dose. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In a fertility and early embryonic development study in female rats, Neratinib was administered orally for 15 days before mating to Day 7 of pregnancy, which did not cause embryonic toxicity at doses up to 12 mg/kg/day in the presence of maternal toxicity. A dose of 12 mg/kg/day in rats is approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m2 basis.

In an embryo-fetal development study in rats, pregnant animals received oral doses of Neratinib up to 15 mg/kg/day during the period of organogenesis. No effects on embryo-fetal development or survival were observed. Maternal toxicity was evident at 15 mg/kg/day (approximately 0.6 times the AUC in patients receiving the maximum recommended dose of 240 mg/day).

In an embryo-fetal development study in rabbits, pregnant animals received oral doses of Neratinib up to 9 mg/kg/day during the period of organogenesis. Administration of Neratinib at doses ≥ 6 mg/kg/day resulted in maternal toxicity, abortions and embryo-fetal death (increased resorptions). Neratinib administration resulted in increased incidence of fetal gross external (domed head), soft tissue (dilation of the brain ventricles and ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities at ≥ 3 mg/kg/day. The AUC(0-t) at 6 mg/kg/day and 9 mg/kg/day in rabbits were approximately 0.5 and 0.8 times, respectively, the AUCs in patients receiving the maximum recommended dose of 240 mg/day.

In a peri and postnatal development study in rats, oral administration of Neratinib from gestation day 7 until lactation day 20 resulted in maternal toxicity at ≥ 10 mg/kg/day (approximately 0.4 times the maximum recommended dose of 240 mg/day in patients on a mg/m2 basis) including decreased body weights, body weight gains, and food consumption. Effects on long-term memory were observed in male offspring at maternal doses ≥ 5 mg/kg/day (approximately 0.2 times the maximum recommended dose of 240 mg/day in patients on a mg/m2 basis).

Lactation

Risk Summary

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 Neratinib, advise lactating women not to breastfeed while taking Neratinib and for at least 1 month after the last dose.

Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, Neratinib can cause fetal harm when administered to a pregnant woman.Females of reproductive potential should have a pregnancy test prior to starting treatment with Neratinib.

Contraception

Females

Based on animal studies, Neratinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Neratinib and for at least 1 month after the last dose.

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Neratinib.

Pediatric Use

The safety and efficacy of Neratinib in pediatric patients has not been established.

Geriatric Use

In the ExteNET trial, the mean age was 52 years in the Neratinib arm; 1236 patients were < 65 years, 172 patients were ≥ 65 years, of whom 25 patients were 75 years or older.

There was a higher frequency of treatment discontinuations due to adverse reactions in the ≥ 65 years age group than in the < 65 years age group; in the Neratinib arm, the percentages were 44.8% compared with 25.2%, respectively, and in the placebo arm 6.4% and 5.3%, respectively.

The incidence of serious adverse reactions in the Neratinib 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 C_{max} and AUC. Reduce the Neratinib dosage for patients with severe hepatic impairment.

CONTRAINDICATION

None

WARNINGS AND PRECAUTION

Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with Neratinib. Diarrhea was reported in 95% of Neratinib -treated patients in ExteNET, a randomized placebo controlled trial. In the Neratinib 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).

Antidiarrheal prophylaxis with loperamide has been shown to lower the incidence and severity of diarrhea. Instruct patients to initiate antidiarrheal prophylaxis with loperamide along with the first dose of Neratinib and continue during the first two cycles (56 days) of treatment.

Monitor patients for diarrhea and treat with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt Neratinib, and reduce subsequent doses. Perform stool cultures 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

Neratinib 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 Neratinib-treated patients. Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with Neratinib 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

Based on findings from animal studies and its mechanism of action, Neratinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of Neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal AUCs approximately 0.2 times the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose.

ADVERSE REACTIONS

The following serious adverse reactions are

- Diarrhea
- Nausea
- Abdominal pain,
- Fatigue
- Vomiting
- Rash
- Stomatitis
- Decreased appetite
- Muscle spasms
- Dyspepsia
- AST or ALT increase
- Nail disorder
- Dry skin

- Abdominal distention
- Weight decreased and urinary tract infection

OVERDOSAGE

There is no specific antidote, and the benefit of hemodialysis in the treatment of Neratinib overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken.
In the clinical trial setting, a limited number of patients reported overdose. The adverse reactions experienced by these patients were diarrhea, nausea, vomiting, and dehydration. The frequency and severity of gastrointestinal disorders (diarrhea, abdominal pain, nausea and vomiting) appear to be dose related.

DRUG INTERACTIONS

Effect of Other Drugs on Neratinib
Table 7 includes drug interactions that affect the pharmacokinetics of Neratinib.

Gastric Acid Reducing Agents		
Clinical Impact	• Concomitant use of Neratinib with a proton pump inhibitor (PPI, lansoprazole) resulted in a decrease of Neratinib Cmax by 71% and AUC by 65%. • Concomitant use with other pH lowering agents was not studied but a decrease in Neratinib AUC is also considered likely. • Decreased Neratinib AUC may reduce Neratinib activity.	
Prevention or Management	• PPIs	Avoid concomitant use .
• H2-receptor antagonists	Avoid concomitant use .	
• Antacids	Separate Neratinib dosing by 3 hours after antacids .	

Strong and Moderate CYP3A4 Inhibitors	
Clinical Impact	• Concomitant use of Neratinib with a strong CYP3A4 inhibitor (ketoconazole) increased Neratinib Cmax by 321% and AUC by

	481%. • Concomitant use of Neratinib 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 Neratinib with strong or moderate CYP3A4 inhibitors.
Examples1	*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 Neratinib with a strong CYP3A4 inducer (rifampin) reduced Neratinib Cmax by 76% and AUC by 87% . • Concomitant use of Neratinib with other strong or moderate CYP3A4 inducers may decrease Neratinib concentrations. • Decreased Neratinib AUC may reduce Neratinib activity.
Prevention or Management	Avoid concomitant use of Neratinib with strong or moderate CYP3A4 inducers.
Examples1	*Strong CYP3A4 inducers:* carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
	Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil

1. These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information

Effect of Neratinib on Other Drugs

P-glycoprotein (P-gp) Substrates

Concomitant use of Neratinib 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. Neratinib may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).

PHARAMCEUTICAL INFORMATION

Storage and Handling

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59–86°F). Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening. Keep out of the reach of children.

Presentation & Packaging

Each commercial box contains 180 flim coated tablets in a bottle