Hernix
Neratinib

COMPOSITION:

Hernix Tablet: Each film coated tablet contains Neratinib Maleate INN equivalent to Neratinib 40 mg

THERAPEUTIC CLASS: Anti Cancer

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.

Pharmacodynamics

Cardiac Electrophysiology

The effect of Neratinib on the QTc interval was evaluated in a randomized, placebo and positive controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 2.4-fold the therapeutic exposures of Neratinib, there was no clinically relevant effect on the QTc interval.

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.

INDICATIONS

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[1]

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 v 4.0

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 Diarrhea[1]	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 features[2] • Grade 2 diarrhea lasting five days or longer[3] • Grade 3 diarrhea lasting longer than 2 days[3]	• 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

[1]Per CTCAE v 4.0
[2]Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia
[3]Despite being treated with optimal medical therapy

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 Hepatoxicity[1]	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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies and the mechanism of action, Neratinib can cause fetal harm when administered to a pregnant woman. Administration of Neratinib during pregnancy may have potential risk to the 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 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 Clinical 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.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Diarrhea: Aggressively manage diarrhea occurring despite recommended prophylaxis with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold Neratinib in patients experiencing severe and/or persistent diarrhea. Permanently discontinue Neratinib in patients experiencing Grade 4 diarrhea or Grade ≥ 2 diarrhea that occurs after maximal dose reduction.

Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold Neratinib in patients experiencing Grade 3 liver abnormalities and permanently discontinue Neratinib in patients experiencing Grade 4 liver abnormalities.

Embryo-Fetal Toxicity: Neratinib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

ADVERSE REACTIONS

The most common adverse reactions (> 5%) were 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.

DRUG INTERACTIONS

Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors (PPI) and H2-receptor antagonists. Separate Neratinib by 3 hours after antacid dosing.

• Strong or moderate CYP3A4 inhibitors: Avoid concomitant use.

• Strong or moderate CYP3A4 inducers: Avoid concomitant use.

• P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with Neratinib.

PHARAMCEUTICAL INFORMATIONS

Storage Conditions

Store at below 30^{0}C and dry place, away from light and moisture. Keep out of the reach of children.

Presentation & Packaging

Hernix Tablet: Each commercial box contains 180 tablets in a bottle.

Only for Export

LF252O1

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh