NERLYNX® (neratinib) Film-Coated Tablets 40 mg

1 INDICATIONS AND USAGE

NERLYNX is indicated for the extended adjuvant treatment of women with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago [*see Clinical Studies (13)*].

2 DOSAGE AND ADMINISTRATION

2.1 Antidiarrheal Prophylaxis

Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of NERLYNX [*see Dosage and Administration (2.3) and Adverse Reactions (6)*].

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

Table 1: Loperamide Prophylaxis

Time on NERLYNX	Dose	Frequency
Weeks 1-2 (days 1 - 14)	4 mg	Three times daily
Weeks 3-4 (days 15 - 28)	4 mg	Twice daily
Weeks 5-8 (days 29 - 56)	4 mg	Twice daily
Weeks 9-52 (days 57 -3 65)	4 mg	As needed (not to exceed 16 mg per day)

NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea [*see Dosage and Administration (2.3)*].

2.2 Recommended Dose and Schedule

The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily with food, continuously for one year.

Instruct patients to take NERLYNX at approximately the same time every day. NERLYNX 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 NERLYNX with the next scheduled daily dose.

2.3 Dose Modifications

Dose Modifications for Adverse Reactions

NERLYNX 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 NERLYNX 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: NERLYNX Dose Modifications for Adverse Reactions

Dose Level	NERLYNX 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: NERLYNX Dose Modifications and Management – General Toxicities[1]

Severity of Toxicity[2]	Action
Grade 3	Hold NERLYNX until recovery to Grade ≤ 1 or baseline within 3 weeks of stopping treatment. Then resume NERLYNX at the next lower dose level.
Grade 4	Discontinue NERLYNX 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 NERLYNX. Guidelines for adjusting doses of NERLYNX 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 NERLYNX 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 NERLYNX 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 NERLYNX treatment at the same dose. • If diarrhea resolves to Grade 0-1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 2). • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.
• Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment

1 Per CTCAE v4.0
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 NERLYNX 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) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)*].

Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of NERLYNX 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 [*see Warnings and Precautions (5.2)*].

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 NERLYNX until recovery to ≤ Grade 1 • Evaluate alternative causes • Resume NERLYNX 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 NERLYNX
• Grade 4 ALT (>20x ULN) OR • Grade 4 bilirubin (>10x ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes

1 Per CTCAE v4.0

Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with NERLYNX [*see Drug Interactions (7.1)*].

H_2-receptor antagonists: Take NERLYNX at least 2 hours before the next dose of the H_2-receptor antagonist or 10 hours after the H_2-receptor antagonist [*see Drug Interactions (7.1)*].

Antacids: Separate dosing of NERLYNX by 3 hours after antacids [*see Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg neratinib (equivalent to 48.31 mg of neratinib maleate).

Film-coated, red, oval shaped and debossed with ‘W104’ on one side and plain on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the inactive ingredients listed in Section 10.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with NERLYNX. Diarrhea was reported in 95% of NERLYNX-treated patients in ExteNET, a randomized placebo controlled trial. In the NERLYNX 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) [*see Adverse Reactions (6.1)*].

Antidiarrheal prophylaxis 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 NERLYNX and continue during the first two cycles (56 days) of treatment [*see Dosage and Administration (2.1)*]. Consider adding other agents to loperamide as clinically indicated [*see Adverse Reactions (6.1)*].

Monitor patients for diarrhea and treat with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt NERLYNX, and reduce subsequent doses [*see Dosage and*

Administration (2.3)]. 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).

5.2 Hepatotoxicity

NERLYNX 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 NERLYNX-treated patients.

Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with NERLYNX 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 [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, NERLYNX 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. [*see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (11.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Diarrhea [*see Warnings and Precautions (5.1)*]
- Hepatotoxicity [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ExteNET

The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. Patients who received NERLYNX in this trial were not required to receive any prophylaxis with antidiarrheal agents to prevent the NERLYNX-related diarrhea. The median duration of treatment was 11.6 months in the NERLYNX arm and 11.8 months in the placebo arm. The median age was 52 years (60% were ≥ 50 years old, 12% were ≥ 65 years old); 81% were Caucasian, 3% Black or African American, 14% Asian and 3% other. A total of 1408 patients were treated with NERLYNX.

NERLYNX dose reduction due to an adverse reaction of any grade occurred in 31.2% of patients receiving NERLYNX compared to 2.6% of patients receiving placebo. Permanent discontinuation due to any adverse reaction was reported in 27.6% of NERLYNX-treated patients. The most common adverse reaction leading to discontinuation was diarrhea, accounting for 16.8% of NERLYNX-treated patients.

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. The most frequently reported Grade 3 or 4 adverse reactions were diarrhea, vomiting, nausea, and abdominal pain.

Serious adverse reactions in the NERLYNX arm included diarrhea (1.6%), vomiting (0.9%), dehydration (0.6%), cellulitis (0.4%), renal failure (0.4%), erysipelas (0.4%), alanine aminotransferase increased (0.3%), aspartate aminotransferase increased (0.3%), nausea (0.3%), fatigue (0.2%), and abdominal pain (0.2%).

Table 6 summarizes the adverse reactions in ExteNET.

Table 6: Adverse Reactions Reported in ≥ 2% of NERLYNX-Treated Patients in ExteNET

System Organ Class (Preferred Term)	NERLYNX n=1408			Placebo n=1408		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhea	95	40	0.1	35	2	0
Nausea	43	2	0	22	0.1	0
Abdominal pain[1]	36	2	0	15	0.4	0
Vomiting	26	3	0	8	0.4	0
Stomatitis[2]	14	0.6	0	6	0.1	0
Dyspepsia	10	0.4	0	4	0	0
Abdominal distension	5	0.3	0	3	0	0
Dry mouth	3	0.1	0	2	0	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	20	0.4	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	9	1	0.2	3	0.2	0
Aspartate aminotransferase increased	7	0.5	0.2	3	0.3	0
Infections and Infestations						
Urinary tract infection	5	0.1	0	2	0	0
Investigations						
Weight decreased	5	0.1	0	0.5	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.2	0	3	0	0
Dehydration	4	0.9	0.1	0.4	0.1	0
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	11	0.1	0	3	0.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5	0	0	1	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[3]	18	0.6	0	9	0	0
Dry skin	6	0	0	2	0	0
Nail Disorder[4]	8	0.3	0	2	0	0
Skin fissures	2	0.1	0	0.1	0	0

[1] Includes abdominal pain, abdominal pain upper, and abdominal pain lower

[2] Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis

[3] Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular, rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption

[4] Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy

CONTROL

CONTROL (NCT02400476) was a multicenter, open-label, multi-cohort trial evaluating patients with early stage HER2-positive breast cancer treated with neratinib 240 mg daily for up to one year receiving loperamide prophylaxis with/without an additional anti-diarrheal treatment. All patients received loperamide 4 mg loading dose, followed by 4 mg three times a day from days 1-14, followed by 4 mg twice a day on days 15-56, followed by loperamide as needed through 1 year of treatment with neratinib [*see Dosage and Administration (2.1)*]. One cohort of patients received budesonide 9 mg once daily on cycle 1 days 1-28, in addition to loperamide. At the interim analysis, the incidence of all grade diarrhea for patients receiving loperamide alone (n=109) was 78% compared to 86% of patients who received budesonide and loperamide (n=64). The incidence of Grade 2 diarrhea was 25% compared to 33%, respectively. The incidence of Grade 3 diarrhea was 32% compared to 28%, respectively. Diarrhea leading to treatment discontinuation occurred in 18% of patients treated with loperamide alone compared to 11% of the patients who received loperamide and budesonide.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NERLYNX

Table 7 includes drug interactions that affect the pharmacokinetics of neratinib.

Table 7: Drug Interactions that Affect Neratinib

Gastric Acid Reducing Agents		
Clinical Impact	Concomitant use of NERLYNX with a proton pump inhibitor, H_2-receptor antagonist, or antacid may decrease neratinib plasma concentration. Decreased neratinib AUC may reduce NERLYNX activity. Lansoprazole (PPI) resulted in a decrease of neratinib C_{max} by 71% and AUC by 65% [*see Clinical Pharmacology (11.3)*].	
Prevention or Management	• PPIs	Avoid concomitant use [*see Dosage and Administration (2.3)*].
	• H_2-receptor antagonists	Take NERLYNX at least 2 hours before the next dose of the H_2-receptor antagonist or 10 hours after the H_2-receptor antagonist [*see Dosage and Administration (2.3)*].
	• Antacids	Separate NERLYNX dosing by 3 hours after antacids [*see Dosage and Administration (2.3)*].

Strong and Moderate CYP3A4 Inhibitors	
Clinical Impact	• Concomitant use of NERLYNX with a strong CYP3A4 inhibitor (ketoconazole) increased neratinib C_{max} by 321% and AUC by 481% [*see Clinical Pharmacology (11.3)*]. • Concomitant use of NERLYNX 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 NERLYNX with strong or moderate CYP3A4 inhibitors.
Examples[1]	*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 NERLYNX with a strong CYP3A4 inducer (rifampin) reduced neratinib C_{max} by 76% and AUC by 87% [*see Clinical Pharmacology (11.3)*]. • Concomitant use of NERLYNX with other strong or moderate CYP3A4 inducers may decrease NERLYNX concentrations. • Decreased neratinib AUC may reduce NERLYNX activity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong or moderate CYP3A4 inducers.
Examples[1]	*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.

7.2 Effect of NERLYNX on Other Drugs

Hormonal contraceptives

It is currently unknown whether Nerlynx reduces the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method.

Breast cancer resistance protein inhibitors

Neratinib may inhibit breast cancer resistance protein (BCRP) moderately as suggested by *in vitro* studies. Clinical studies with BCRP substrates have not been conducted. Patients who are treated with BCRP inhibitors (e.g., rosuvastatin and sulfasalazine) should be monitored carefully.

P-glycoprotein (P-gp) Substrates

Concomitant use of NERLYNX with digoxin, a P-gp substrate, increased digoxin concentrations [*see Clinical Pharmacology (11.3)*]. 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. NERLYNX may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (11.1)*].

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 (*see Data*). 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/m^2 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 $AUC_{(0\text{-}t)}$ 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/m^2 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/m^2 basis).

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

8.3 Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with NERLYNX.

Contraception

Females

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with NERLYNX 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 NERLYNX [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

In the ExteNET trial, the mean age was 52 years in the NERLYNX 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 NERLYNX 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 NERLYNX 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%).

8.6 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 NERLYNX dosage for patients with severe hepatic impairment. [*see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)*].

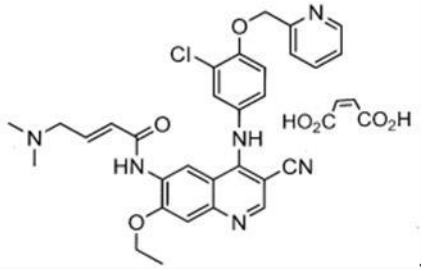
9 OVERDOSAGE

There is no specific antidote, and the benefit of hemodialysis in the treatment of NERLYNX 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.

10 DESCRIPTION

NERLYNX (neratinib) immediate release, film-coated tablets for oral administration contain 40 mg of neratinib, equivalent to 48.31 mg neratinib maleate. Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors. The molecular formula for neratinib maleate is $C_{30}H_{29}ClN_6O_3 \bullet C_4H_4O_4$ and the molecular weight is 673.11 Daltons. The chemical name is (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate, and its structural formula is:



Neratinib maleate is an off-white to yellow powder with pK_as of 7.65 and 4.66. The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH. Neratinib maleate is sparingly soluble at pH 1.2 (32.90 mg/mL) and insoluble at approximate pH 5.0 and above (0.08 mg/mL or less).

Inactive ingredients: Tablet Core: colloidal silicon dioxide, mannitol, microcrystalline cellulose, crospovidone, povidone, magnesium stearate & purified water. Coating: red film coat: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red.

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents, protein kinase inhibitor, ATC code: L01XE45.

11 CLINICAL PHARMACOLOGY

11.1 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.

11.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NERLYNX 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 NERLYNX, there was no clinically relevant effect on the QTc interval.

11.3 Pharmacokinetics

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.

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.

Effect of Food

The food-effect assessment was conducted in healthy volunteers who received NERLYNX 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. [*See Dosage and Administration (2.2)*]

Distribution

In patients, following multiple doses of NERLYNX, the mean (%CV) apparent volume of distribution at steady-state (V_{ss}/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 NERLYNX 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 NERLYNX 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 NERLYNX, neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of NERLYNX 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.

Patients with Hepatic Impairment

Neratinib is mainly metabolized in the liver. Single doses of 120 mg NERLYNX 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. [*see Dosage and Administration (2.3) and Use in Specific Populations (8.6)*].

Drug Interaction Studies

Gastric Acid Reducing Agents: NERLYNX solubility decreases with increasing GI tract pH values. Drugs that alter the pH values of the GI tract may alter the solubility of neratinib and hence its absorption and systemic exposure. When multiple doses of lansoprazole (30 mg daily), a proton pump inhibitor, were co-administered with a single 240 mg oral doses of NERLYNX, the neratinib C_{max} and AUC decreased by 71% and 65%, respectively. When a single oral dose of 240 mg NERLYNX was administered 2 hours following a daily dose of 300 mg ranitidine, an H_2-receptor antagonist, the neratinib C_{max} and AUC were reduced by 57% and 48%, respectively. When a single oral dose of 240 mg NERLYNX was administered 2 hours prior to 150 mg ranitidine twice daily (administered in the morning and evening, approximately 12 hours apart), the neratinib C_{max} and AUC were reduced by 44% and 32%, respectively. [*See Dosage and Administration (2.3) and Drug Interactions (7.1)*].

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 NERLYNX 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 NERLYNX safety from concomitant use with moderate CYP3A4 inhibitors warrants consideration [*see Drug Interactions (7.1)*].

Strong and Moderate CYP3A4 Inducers: Concomitant use of rifampin, a strong inducer of CYP3A4, with a single oral 240 mg NERLYNX 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 NERLYNX 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 NERLYNX efficacy from concomitant use with moderate CYP3A4 inducers warrants consideration [*see Drug Interactions (7.1)*].

Effect of NERLYNX on P-gp Transporters: Concomitant use of digoxin (a single 0.5 mg oral dose), a P-gp substrate, with multiple oral doses of NERLYNX 240 mg in healthy subjects (n=18) increased the mean digoxin C_{max} by 54% and AUC by 32% [*see Drug Interactions (7.2)*].

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral neratinib doses of 1, 3, and 10 mg/kg/day. Neratinib was not carcinogenic in male and female rats at exposure levels > 25 times the AUC in patients receiving the maximum recommended dose of 240 mg/day. Neratinib was not carcinogenic in a 26-week study in Tg.rasH2 transgenic mice when administered daily by oral gavage at doses up to 50 mg/kg/day in males and 125 mg/kg/day in females.

Neratinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

In a fertility study in rats, neratinib administration up to 12 mg/kg/day (approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis) caused no effects on mating or the ability of animals to become pregnant. In repeat-dose toxicity studies in dogs with oral administration of neratinib daily for up to 39 weeks, tubular hypoplasia of the testes was observed at ≥ 0.5 mg/kg/day. This finding was observed at AUCs that were approximately 0.4 times the AUC in patients at the maximum recommended dose of 240 mg.

13 CLINICAL STUDIES

13.1 Extended Adjuvant Treatment in Breast Cancer

The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX after adjuvant treatment with a trastuzumab based therapy in women with HER2-positive breast cancer.

A total of 2840 patients with early-stage (Stage 1 to 3c) HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. NERLYNX 240 mg or placebo was given orally once daily for one year. The major efficacy outcome measure was invasive disease-free survival (iDFS) defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up.

Patient demographics and tumor characteristics were generally balanced between treatment arms. Patients had a median age of 52 years (range 23 to 83) and 12% of patients were 65 or older. The majority of patients were White (81%), and most patients (99.7%) had an ECOG performance status of 0 or 1. Fifty-seven percent (57%) of patients had hormone receptor positive disease (defined as ER-positive and/or PR-positive), 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. Ten percent (10%) of patients had Stage I disease, 41% had Stage II disease and 31% had Stage III disease. The majority of patients (81%) were enrolled within one year of completion of trastuzumab treatment. Median time from the last adjuvant trastuzumab treatment to randomization was 4.4 months in the NERLYNX arm versus 4.6 months in the placebo arm. Median duration of treatment was 11.6 months in the NERLYNX arm vs. 11.8 months in the placebo arm.

The efficacy results from the ExteNET trial are summarized in Table 8 and Figure 1.

Table 8. Efficacy iDFS Results for the ITT Population

Number of Events/ Total N (%)		**iDFS at 24 months* (%, 95% CI)**		**Stratified† HR (95% CI)**	**P-value‡**
NERLYNX	Placebo	NERLYNX	Placebo		
67/1420 (4.7)	106/1420 (7.5)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	0.66 (0.49, 0.90)	0.008

CI= Confidence Interval; HR=Hazard Ratio; iDFS=Invasive Disease Free-Survival; ITT=Intent to Treat

* Kaplan-Meier estimate

† Stratified by prior trastuzumab (concurrent vs. sequential), nodal status (0-3 positive nodes vs. ≥4 positive nodes), and ER/PR status (positive vs. negative)

‡ Stratified log-rank test

Figure 1 iDFS in the ExteNET Trial - ITT population

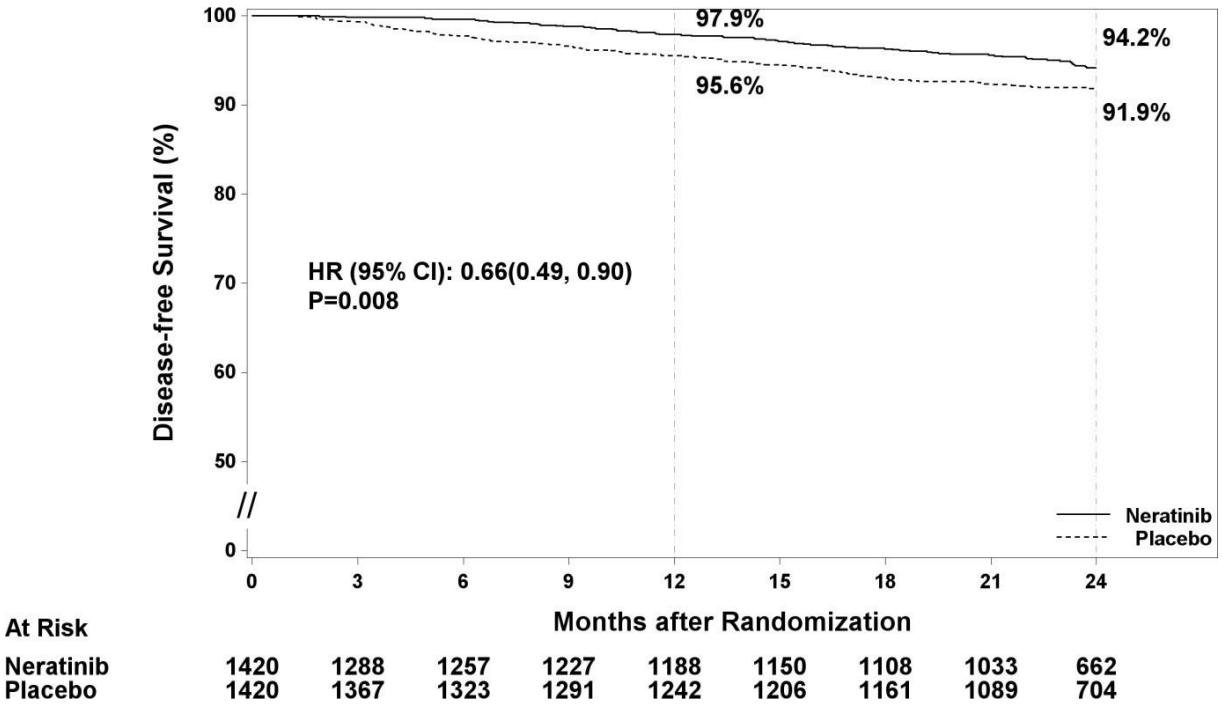


Table 9: Subgroup Analyses[*]

Population	Number of Events/Total N (%)		iDFS at 24 months[†] (%, 95% CI)		Unstratified HR (95% CI)
	NERLYNX	**Placebo**	**NERLYNX**	**Placebo**	
Hormone Receptor Status					
Positive	29/816 (3.6)	63/815 (7.7)	95.6 (93.8, 96.9)	91.5 (89.2, 93.3)	0.49 (0.31, 0.75)
Negative	38/604 (6.3)	43/605 (7.1)	92.2 (89.4, 94.3)	92.4 (89.8, 94.3)	0.93 (0.60, 1.43)
Nodal Status					
Negative	7/335 (2.1)	11/336 (3.3)	97.2 (94.1, 98.7)	96.5 (93.7, 98.0)	0.72 (0.26, 1.83)
1-3 Positive Nodes	31/664 (4.7)	47/664 (7.1)	94.4 (92.2, 96.1)	92.4 (90.0, 94.2)	0.68 (0.43, 1.07)
≥4 Positive Nodes	29/421 (6.9)	48/420 (11.4)	91.4 (87.9, 94.0)	87.3 (83.4, 90.2)	0.62 (0.39, 0.97)

Population	Number of Events/Total N (%)		iDFS at 24 months† (%, 95% CI)		Unstratified HR (95% CI)
Prior Trastuzumab					
Concurrent	49/884 (5.5)	66/886 (7.4)	93.2 (91.0, 94.8)	92.0 (89.9, 93.7)	0.80 (0.55, 1.16)
Sequential	18/536 (3.4)	40/534 (7.5)	95.8 (93.4, 97.3)	91.6 (88.7, 93.8)	0.46 (0.26, 0.78)
Completion of Prior Trastuzumab					
≤1 year	58/1152 (5.0)	95/1145 (8.3)	93.8 (92.0, 95.2)	90.9 (89.0, 92.5)	0.63 (0.45, 0.88)
1-2 years	9/262 (3.4)	11/270 (4.1)	95.8 (92.0, 97.8)	95.7 (92.3, 97.6)	0.92 (0.37, 2.22)

CI=Confidence Interval; HR=Hazard Ratio

* Exploratory analyses without adjusting multiple comparisons

† Kaplan-Meier estimate

Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. This exploratory analysis suggests that the iDFS results at 5 years are consistent with the 2-year iDFS results observed in ExteNET. At the time of the iDFS analysis, 2% of patients had died, and overall survival data were immature.

14 HOW SUPPLIED/STORAGE AND HANDLING

NERLYNX 40 mg film-coated tablets are red, oval shaped and debossed with ‘W104’ on one side and plain on the other side.

NERLYNX is available in: Bottles of 180 tablets:

Store at 30ºC or below. Keep the bottle tightly closed. Protect from moisture.

The bottle contains a desiccant canister. Do not swallow the canister

15 PATIENT COUNSELING INFORMATION

Diarrhea

- Inform patients that NERLYNX has been associated with diarrhea which may be severe in some cases.
- Instruct patients to maintain 1-2 bowel movements per day and on how to use anti-diarrheal treatment regimens.
- Advise patients to inform their healthcare provider immediately if severe (≥Grade 3) diarrhea or diarrhea associated with weakness, dizziness, or fever occurs during treatment with NERLYNX [*see Dosage and Administration (2.1) and Warnings and Precautions (5.1)*].

Hepatotoxicity

- Inform patients that NERLYNX has been associated with hepatotoxicity which may be severe in some cases.
- Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately [*see Warnings and Precautions (5.2)*].

Embryo-Fetal Toxicity

- Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [*see Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment and for 1 month after receiving the last dose of NERLYNX [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)*].
- Advise lactating women not to breastfeed during treatment with NERLYNX and for at least 1 month after the last dose [*see Use in Specific Populations (8.2)*].

Drug Interactions

- NERLYNX may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products [*see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)*].
- NERLYNX may interact with gastric acid reducing agents. Advise patients to avoid concomitant use of proton pump inhibitors. When patients require gastric acid reducing agents, use an H_2-receptor antagonist or antacid. Advise patients to separate the dosing of NERLYNX by 3 hours after antacid medicine, and to take NERLYNX at least 2 hours before or 10 hours after a H_2-receptor antagonist. [*see Dosage and Administration (2.3) and Drug Interactions (7.1)*].
- NERLYNX may interact with grapefruit. Advise patients to avoid taking NERLYNX with grapefruit products [*see Drug Interactions (7.1)*].

Dosing and Administration

- Instruct patients to take NERLYNX with food at approximately the same time each day consecutively for one year.
- If a patient misses a dose, instruct the patient not to replace the missed dose, and to resume NERLYNX with the next scheduled daily dose [*see Dosage and Administration (2.2)*].

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