

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **NERLYNX**<sup>®</sup>

Neratinib Tablets

40 mg neratinib (as neratinib maleate), Oral

Protein Kinase Inhibitor (L01XE45)

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

NERLYNX (neratinib) is indicated for the extended adjuvant treatment of women with early-stage hormone receptor positive, HER2-overexpressed/amplified breast cancer within one year after completion of trastuzumab-based adjuvant therapy.

#### 1.1 Pediatrics

**Pediatrics (<18 years of age):** The safety and efficacy of NERLYNX in children and adolescents <18 years have not been established.

#### 1.2 Geriatrics

**Geriatrics (≥ 65 years of age):** Of 1408 patients who received NERLYNX in the Phase 3 study (ExteNET), 24.9% were ≥ 60 years of age. Lower magnitude of efficacy was noted in patients of ≥ 60 years when compared to patients of <60 years of age. Some differences in the clinical safety have been identified between the elderly and younger subjects (see WARNING AND PRECAUTIONS, Geriatrics).

### 2 CONTRAINDICATIONS

NERLYNX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

### 3 DOSAGE AND ADMINISTRATION

#### 3.1 Dosing Considerations

##### Antidiarrheal Prophylaxis

NERLYNX treatment can cause severe diarrhea (see WARNING AND PRECAUTIONS). Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of NERLYNX (see WARNINGS AND PRECAUTIONS).

Instruct patients to take loperamide as directed in [Table 1](#), titrating to 1-2 bowel movements per day. Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. NERLYNX dose interruptions and dose reductions may be required to manage diarrhea (see [Table 4](#) below).

**Table 1. Loperamide Prophylaxis**

| Time on NERLYNX            | 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 16 mg per day) |

**3.2 Recommended Dose and Dosage Adjustment**

The recommended dose of NERLYNX is 240 mg (six 40 mg tablets) given orally once daily with food, continuously for one year at approximately the same time every day. High-fat meal may lead to higher exposures of NERLYNX than a standard breakfast (see DRUG INTERACTIONS, Drug-Food Interactions).

NERLYNX tablets should be swallowed whole with a glass of water (tablets should not be chewed, crushed or split prior to swallowing).

NERLYNX should be used in combination with endocrine therapy in patients with early-stage hormone receptor-positive and HER2 overexpressed/amplified breast cancer within one year after completion of trastuzumab-based adjuvant therapy.

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 of treatment with NERLYNX as shown in [Tables 2 to 5](#) below. Discontinue NERLYNX in patients who fail to recover to Grade 0-1 from treatment-related toxicity, for toxicities that result in a treatment delay of > 3 weeks, or for patients who are unable to tolerate 120 mg NERLYNX 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\***

| Severity of Toxicity <sup>†</sup> | 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.   |

\* Refer to [Table 4](#) and [Table 5](#) below for management of diarrhea and hepatotoxicity

† 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 patients presenting with diarrhea are shown in [Table 4](#).

**Table 4. Dose Modifications for Diarrhea**

| Severity of Diarrhea *  | Action   |
|---|--|
| <ul style="list-style-type: none"> <li>Grade 1 diarrhea [increase of &lt; 4 stools per day over baseline]</li> <li>Grade 2 diarrhea [increase of 4-6 stools per day over baseline] lasting &lt; 5 days</li> <li>Grade 3 diarrhea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤ 2 days</li> </ul> | <ul style="list-style-type: none"> <li>Adjust antidiarrheal treatment</li> <li>Diet modifications</li> <li>Fluid intake of ~2 L should be maintained to avoid dehydration</li> <li>Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.</li> </ul>   |
| <ul style="list-style-type: none"> <li>Any grade with complicated features<sup>†</sup></li> <li>Grade 2 diarrhea lasting 5 days or longer<sup>†</sup></li> <li>Grade 3 diarrhea lasting longer than 2 days<sup>†</sup></li> </ul>   | <ul style="list-style-type: none"> <li>Interrupt NERLYNX treatment</li> <li>Diet modifications</li> <li>Fluid intake of ~2 L should be maintained to avoid dehydration</li> <li>If diarrhea resolves to Grade 0-1 in one week or less, then resume NERLYNX treatment at the same dose.</li> <li>If diarrhea resolves to Grade 0-1 in longer than one week, then resume NERLYNX treatment at reduced dose (see <a href="#">Table 2</a>).</li> <li>Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.</li> </ul> |

| Severity of Diarrhea *  | Action  |
|---|---|
| <ul style="list-style-type: none"> <li>Grade 4 diarrhea [life-threatening consequences; urgent intervention indicated]</li> <li>Diarrhea recurs to Grade 2 or higher at 120 mg per day</li> </ul> | <ul style="list-style-type: none"> <li>Permanently discontinue NERLYNX treatment</li> </ul> |

\* Per CTCAE v4.0

† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia

‡ Despite being treated with optimal medical therapy

### Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of NERLYNX in the event of liver toxicity are shown in Table 5. Patients who experience  $\geq$  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).

**Table 5. Dose Modification for Hepatotoxicity**

| Severity of Hepatotoxicity *  | Action  |
|---|---|
| <ul style="list-style-type: none"> <li>Grade 3 ALT or AST (&gt;5-20x ULN)<br/>OR</li> <li>Grade 3 bilirubin (&gt;3-10x ULN)</li> </ul>  | <ul style="list-style-type: none"> <li>Hold NERLYNX until recovery to <math>\leq</math> Grade 1</li> <li>Resume NERLYNX at the next lower dose level if recovery to <math>\leq</math> Grade 1 occurs within 3 weeks. If Grade 3 ALT, AST or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX</li> </ul> |
| <ul style="list-style-type: none"> <li>Grade 4 ALT or AST (&gt;20x ULN)<br/>OR</li> <li>Grade 4 bilirubin (&gt;10x ULN)</li> </ul>  | <ul style="list-style-type: none"> <li>Permanently discontinue NERLYNX</li> </ul>   |
| Signs or symptoms related to liver injury with either: <ul style="list-style-type: none"> <li>Grade 2 ALT or AST (&gt;2.5-5x ULN)<br/>OR</li> <li>Grade 2 bilirubin (&gt;1.5-3x ULN)</li> </ul> |   |
| ALT or AST >3x ULN and bilirubin >2x ULN and alkaline phosphatase <2x ULN (potentially Hy's Law indicators of drug-induced liver damage)  |   |

ULN=Upper Limit Normal; ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase

\* Per CTCAE v4.0

### Dose Modifications for Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. NERLYNX has not been studied in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

### 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 WARNINGS AND PRECAUTIONS, Hepatotoxicity and ACTION AND CLINICAL PHARMACOLOGY).

### Pediatrics (< 18 years old)

The safety and efficacy of NERLYNX in the pediatric population have not been established. No data are available to support the use of NERLYNX in pediatric patients.

### Geriatrics (≥ 65 years old)

No dose adjustment of NERLYNX is required in patients of ≥ 65 years of age. Older patients may experience higher toxicity and/or lower tolerance to NERLYNX treatment (see WARNINGS and PRECAUTIONS).

### **3.3 Missed Dose**

If a patient misses a dose, do not replace missed dose, and instruct the patient to resume NERLYNX with the next scheduled daily dose.

## **4 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 of NERLYNX 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.

**For management of a suspected drug overdose, contact your regional Poison Control Centre.**



## 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6. Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition  | Non-medicinal Ingredients  |
|-------------------------|---|--|
| Oral                    | Tablet, 40 mg neratinib (equivalent to 48.3 mg neratinib maleate).<br><br>NERLYNX tablets are supplied as red, oval shaped and debossed, film-coated 40 mg tablets with 'W104' on one side and plain on the other side. | Tablet core: colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, povidone, and purified water.<br><br>Film coating: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide. |

### Packaging

NERLYNX is available in white, opaque round HDPE bottles, containing 180 tablets, with a child-resistant closure and foil-lined induction seal. An HDPE desiccant canister with 1 g silica gel is enclosed with the drug product in each container.

## 6 WARNINGS AND PRECAUTIONS

### Cardiovascular

#### Decreased Left Ventricular Function

In a randomized, placebo-controlled study (ExteNET trial), patients with left ventricular ejection fraction (LVEF) either below institutional lower limit of normal or below 50%, symptomatic congestive heart failure of NYHA class 2 or higher, QTcF > 450 msec, ventricular arrhythmia requiring medical therapy, or with a history of myocardial infarction within 12 months were excluded from the study. Grade 3 ejection fraction decreased or congestive cardiac failure was reported in 5 (0.4%) patients in the NERLYNX arm and 2 (0.1%) patients in the placebo arm. In the NERLYNX arm, 15 (1.1%) patients discontinued treatment due to decreased ejection fraction or left ventricular dysfunction versus 6 (0.4%) patients in the placebo arm. In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.

### Gastrointestinal

#### Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with NERLYNX. In the ExteNET trial, diarrhea of any grade occurred in 95% of NERLYNX-treated patients. Grade 3 diarrhea occurred in 40% and Grade 4 diarrhea occurred in 0.1% of NERLYNX-treated patient (see ADVERSE REACTIONS). The majority of patients (93%) had diarrhea in the first month of treatment, the median time to the first onset of Grade  $\geq$  3 diarrhea was 8 days (range: 1-350 days). The median cumulative duration of Grade  $\geq$

3 diarrhea was 5 days (range: 1-139 days). NERLYNX treatment was discontinued in 17% of patients due to diarrhea.

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 NERLYNX and continue during the first two months (56 days) of treatment (see DOSAGE AND ADMINISTRATION). In addition, start proactive management of diarrhea at the first sign of diarrhea especially within the first 2 weeks of starting NERLYNX, including adequate oral hydration, avoid of foods that might aggravate the diarrhea, and treat with additional antidiarrheal therapy as needed.

When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt NERLYNX and reduce subsequent doses. Permanently discontinue NERLYNX in patients with diarrhea recurring to  $\geq$  Grade 2 at 120 mg NERLYNX daily dose or with Grade 4 diarrhea (see DOSAGE AND ADMINISTRATION). 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).

## **Hepatic / Biliary / Pancreatic**

### Hepatotoxicity

NERLYNX has been associated with hepatotoxicity, characterized by increased liver enzymes. In the ExteNET trial, 12% of patients treated with NERLYNX reported hepatotoxicity including 5% of patients experienced an alanine aminotransferase (ALT) increase or an aspartate aminotransferase (AST) increase  $\geq$  3x ULN ( $\geq$  Grade 2). Of those, 1.7% of patients experienced an AST or ALT elevation  $>$  5x ULN ( $\geq$  Grade 3). Increased bilirubin was reported in 1% of patients. Hepatotoxicity or increases in liver transaminases led to a drug discontinuation in 1.7% of NERLYNX-treated patients. The median time of onset to any hepatotoxicity was 31 (range: 1-358) days.

Liver function tests should be conducted prior to and during NERLYNX treatment (see Monitoring and Laboratory Tests below). Dose modifications are recommended for patients with treatment-emergent hepatotoxicity (see Dosage and Administration). NERLYNX treatment should be permanently discontinued in patients with Grade 4 increased in liver transaminases ( $>$ 20x ULN), Grade 4 bilirubin ( $>$ 10x ULN), or in those with ALT/AST  $\geq$  3x ULN and bilirubin  $>$  2x ULN (see Dosage and Administration).

## **Monitoring and Laboratory Tests**

### Liver Function Monitoring

Liver function tests including total bilirubin, ALT, AST, and alkaline phosphatase should be measured prior to starting treatment with NERLYNX and 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. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation (see DOSAGE AND ADMINISTRATION, Dose Modifications for Hepatotoxicity and ADVERSE REACTIONS).

## Left Ventricular Function Testing

In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.

## **Sexual Health**

### Reproduction

Women of childbearing potential must be advised to avoid pregnancy while on NERLYNX. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 1 month after the last dose (see NON-CLINICAL TOXICOLOGY). Pregnancy testing is recommended for women of reproductive potential prior to starting treatment with NERLYNX.

Men with female partners of reproductive potential should be advised to use effective contraception during treatment with NERLYNX and for 3 months after the final dose.

### Fertility

Fertility studies in humans have not been performed with NERLYNX. In a fertility study in rats, neratinib caused no effects on mating or the ability of animals to become pregnant; however, effects on male reproductive organs were observed in chronic, repeated-dose toxicity studies (see NON-CLINICAL TOXICOLOGY).

## **6.1 Special Populations**

### **6.1.1 Pregnant Women**

There are no data regarding the use of NERLYNX in pregnant women. In animal studies, administration of neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities at maternal exposures approximately 0.2 times the exposure in patients receiving the recommended dose (see NON-CLINICAL TOXICOLOGY). Based on its mechanism of action and findings from nonclinical reproduction studies, NERLYNX can cause fetal harm when administered to a pregnant woman.

NERLYNX is not recommended during pregnancy and in women of childbearing potential not using effective contraception. If the patient becomes pregnant while taking NERLYNX, the patient should be informed of the potential hazard to the fetus.

### **6.1.2 Breast-feeding**

It is unknown if neratinib or its metabolites are excreted in human milk. As many drugs are excreted in human milk, and 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 (see NON-CLINICAL TOXICOLOGY).

### **6.1.3 Pediatrics**

No data are available to Health Canada, therefore Health Canada has not authorized an indication for pediatric use.

### 6.1.4 Geriatrics

In the ExteNET trial, the mean age was 52 years in the NERLYNX arm; 12% were  $\geq 65$  years including 2% who were 75 years or older.

In the NERLYNX arm, a greater percentage of older patients (45%) compared with younger patients (25%) experienced treatment discontinuation due to adverse reactions. Diarrhea was the most common adverse reaction leading to treatment discontinuation, which was reported in 29% of older patients and 15% of younger patients.

The incidence of serious adverse reactions in the NERLYNX arm was 7.0% in the  $< 65$  years-old group and 9.9% in the  $\geq 65$  years-old group. The serious adverse reactions most frequently reported in the  $\geq 65$  years-old group were vomiting (2.3%), diarrhea (1.7%), renal failure (1.7%), and dehydration (1.2%).

## 7 ADVERSE REACTIONS

### 7.1 Adverse Reaction Overview

In the randomized, double blind, placebo-controlled study (ExteNET) in women with HER2-positive early-stage breast cancer after completion of trastuzumab-based adjuvant therapy, patients were treated with NERLYNX or placebo for one year. The median duration of treatment was similar between the two arms: 11.6 (range: 0.03 - 13.3) months in the NERLYNX arm and 11.8 (range: 0.13 - 13.2) months in the placebo arm.

Patients treated with NERLYNX experienced higher incidences of treatment-emergent adverse events (99% vs 88%), grade 3-4 adverse events (50% vs 13%), and treatment-related adverse events (96% vs 57%) than those treated with placebo.

In the NERLYNX arm, the most common adverse reactions ( $\geq 10\%$ ) were diarrhea (95%), nausea (43%), abdominal pain (36%), fatigue (27%), vomiting (26%), rash (18%), stomatitis (14%), decreased appetite (12%), muscle spasms (11%), and dyspepsia (10%).

Serious adverse reactions were reported in 7% of patients treated with NERLYNX and 6% of patients treated with placebo. Serious adverse reactions reported in  $\geq 3$  patients 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%).

NERLYNX dose reduction and dose interruption due to an adverse reaction occurred in 31.2% and 45% of patients, respectively. 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.

### 7.2 Clinical Trial Adverse Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

ExteNET

Table 7 summarizes the incidence rates of adverse drug reactions occurring at  $\geq 2\%$  of patients and with higher incidences reported in the NERLYNX arm in the ExteNET trial. Patients who received NERLYNX in this trial were not required to receive any prophylaxis with antidiarrheal agents to prevent the NERLYNX-related diarrhea.

**Table 7. Incidence Rate of Adverse Reactions Reported in  $\geq 2\%$  of Patients treated with NERLYNX and with Higher Incidence Rates in the NERLYNX arm in ExteNET Study**

| System Organ Class<br>(Preferred Term)                      | NERLYNX<br>n=1408 |                |                | Placebo<br>n=1408 |                |                |
|---|-------------------|----------------|----------------|-------------------|----------------|----------------|
|   | All Grades<br>(%) | Grade 3<br>(%) | Grade 4<br>(%) | All Grades<br>(%) | Grade 3<br>(%) | Grade 4<br>(%) |
| <b>Gastrointestinal Disorders</b>                           |                   |                |                |                   |                |                |
| Diarrhea  | 95                | 40             | 0.1            | 35                | 2              | 0              |
| Nausea  | 43                | 2              | 0              | 22                | 0.1            | 0              |
| Abdominal pain*   | 36                | 2              | 0              | 15                | 0.4            | 0              |
| Vomiting  | 26                | 3              | 0              | 8                 | 0.4            | 0              |
| Stomatitis <sup>†</sup>                                     | 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              |
| Flatulence  | 5                 | 0.1            | 0              | 3                 | 0.1            | 0              |
| Dry mouth   | 3                 | 0.1            | 0              | 2                 | 0              | 0              |
| Hemorrhoids   | 2                 | 0              | 0              | 1                 | 0              | 0              |
| <b>General Disorders and Administration Site Conditions</b> |                   |                |                |                   |                |                |
| Fatigue   | 27                | 2              | 0              | 20                | 0.4            | 0              |
| Pyrexia   | 6                 | 0              | 0              | 4                 | 0              | 0              |
| <b>Hepatobiliary Disorders</b>                              |                   |                |                |                   |                |                |
| Alanine aminotransferase increased                          | 9                 | 1              | 0.2            | 3                 | 0.2            | 0              |
| Aspartate aminotransferase increased                        | 7                 | 0.5            | 0.2            | 3                 | 0.3            | 0              |
| <b>Infections and Infestations</b>                          |                   |                |                |                   |                |                |
| Urinary tract infection                                     | 5                 | 0.1            | 0              | 2                 | 0              | 0              |
| Cystitis  | 3                 | 0              | 0              | 1                 | 0              | 0              |
| <b>Investigations</b>                                       |                   |                |                |                   |                |                |
| Weight decreased  | 5                 | 0.1            | 0              | 0.5               | 0              | 0              |
| <b>Metabolism and Nutrition Disorders</b>                   |                   |                |                |                   |                |                |
| Decreased appetite  | 12                | 0.2            | 0              | 3                 | 0              | 0              |
| Dehydration   | 4                 | 0.9            | 0.1            | 0.4               | 0.1            | 0              |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |                   |                |                |                   |                |                |
| Muscle spasms   | 11                | 0.1            | 0              | 3                 | 0.1            | 0              |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      |                   |                |                |                   |                |                |
| Epistaxis   | 5                 | 0              | 0              | 1                 | 0.1            | 0              |
| <b>Skin and Subcutaneous Tissue Disorders</b>               |                   |                |                |                   |                |                |
| Rash <sup>‡</sup>   | 21                | 0.6            | 0              | 10                | 0.1            | 0              |

| System Organ Class<br>(Preferred Term) | NERLYNX<br>n=1408 |                |                | Placebo<br>n=1408 |                |                |
|--|-------------------|----------------|----------------|-------------------|----------------|----------------|
|  | All Grades<br>(%) | Grade 3<br>(%) | Grade 4<br>(%) | All Grades<br>(%) | Grade 3<br>(%) | Grade 4<br>(%) |
| Dry skin                               | 6                 | 0              | 0              | 2                 | 0              | 0              |
| Nail Disorder <sup>§</sup>             | 8                 | 0.3            | 0              | 2                 | 0              | 0              |
| Skin fissures                          | 2                 | 0.1            | 0              | 0.1               | 0              | 0              |

\* Includes abdominal pain, abdominal pain upper, and abdominal pain lower

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

‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular, rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption, erythema multiforme, exfoliative rash, and acne

§ Includes nail disorder, paronychia, onychoclasia, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy

### 7.3 Less Common Clinical Trial Adverse Reactions

The following treatment emergent adverse reactions were reported in less than 2% of patients and with higher incidences in the NERLYNX arm in the ExteNET study.

**Gastrointestinal Disorders:** gastroesophageal reflux disease (1.8%), gastritis (1.4%), gastrointestinal pain (1.1%).

**General Disorders and Administration Site Conditions:** chills (1.8%), malaise (1.8%),

**Hepatobiliary Disorders:** blood alkaline phosphatase increased (2%), hyperbilirubinemia (0.7%), cholelithiasis (0.5%).

**Infections and Infestations:** cellulitis (1.7%).

**Renal and Urinary Disorders:** dysuria (1.8%), renal failure and renal failure acute (0.6%), blood creatinine increased (1.0%).

**Respiratory, thoracic and mediastinal disorders:** rhinorrhoea (1.4%), nasal dryness (1.4%).

**Skin and Subcutaneous Tissue Disorders:** palmar-plantar erythrodysesthesia syndrome (1.8%), skin disorder (1%).

## 7.4 Laboratory Abnormalities

**Table 7: Laboratory Abnormalities Reported in ≥ 10% of Patients Treated with NERLYNX in ExteNET Study**

| Laboratory Tests                     | NERLYNX<br>n=1408 |             |             | Placebo<br>n=1408 |             |             |
|--------------------------------------|-------------------|-------------|-------------|-------------------|-------------|-------------|
|                                      | All Grades (%)    | Grade 3 (%) | Grade 4 (%) | All Grades (%)    | Grade 3 (%) | Grade 4 (%) |
| <b>Chemistry</b>                     |                   |             |             |                   |             |             |
| Alanine Aminotransferase increased   | 35                | 2           | 0.2         | 23                | 0.4         | 0.1         |
| Alkaline Phosphatase increased       | 21                | 0           | 0           | 24                | 0.1         | 0           |
| Aspartate Aminotransferase increased | 26                | 0.8         | 0.1         | 18                | 0.4         | 0.1         |
| Bilirubin increased                  | 10                | 0.1         | 0.0         | 11                | 0.4         | 0.1         |
| Creatinine increased                 | 11                | 0.1         | 0.1         | 8                 | 0           | 0           |
| <b>Hematology</b>                    |                   |             |             |                   |             |             |
| Hemoglobin decreased                 | 35                | 0.2         | 0.4         | 23                | 0           | 0.4         |

\* Grades using NCI CTCAE version 3.0.

## 8 DRUG INTERACTIONS

### 8.1 Overview

Neratinib is primarily metabolized in the liver by CYP3A4. It is also a substrate of P-glycoprotein (P-gp). Drug interactions were observed when NERLYNX was coadministered with a strong CYP3A4/P-gp inhibitor and a strong CYP3A4/P-gp inducer. Concomitant use of NERLYNX with a moderate CYP3A4/P-gp inhibitor is predicted to significantly increase neratinib plasma concentrations. The relative contributions of CYP3A4 and P-gp to the pharmacokinetics of neratinib are unknown. The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH. Drug interactions were observed when NERLYNX was coadministered with a proton pump inhibitor (PPI) and a H2-receptor antagonist under fed conditions.

Neratinib may inhibit the transport of P-gp substrate, and increase the exposure of co-administered medicinal products primarily cleared by P-gp.

### 8.2 Drug-Drug Interactions

The drugs listed in [Table 8](#) are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

**Table 8. Established or Potential Drug-Drug Interactions**

| Common name  | Source of Evidence | Effect   | Clinical comment  |
|--|--------------------|--|---|
| <b>Pharmacokinetic Interactions (Drugs that may affect the exposure to neratinib)</b>  |                    |  |   |
| Strong inhibitor of CYP3A4/P-gp (e.g., boceprevir, clarithromycin, cobicistat, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, tipranavir, troleandomycin, voriconazole) | CT                 | Concomitant use of NERLYNX with a strong CYP3A4/P-gp inhibitor (ketoconazole) increased neratinib $C_{max}$ by 321% and AUC by 481%.   | Avoid concomitant use of NERLYNX with strong CYP3A4 and/or P-gp inhibitors.   |
| Moderate inhibitor of CYP3A4/P-gp (e.g., aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil)  | T                  | Concomitant use of NERLYNX with a moderate CYP3A4/P-gp inhibitor may significantly increase neratinib exposure.  | Avoid concomitant use of NERLYNX with moderate CYP3A4 and/or P-gp inhibitors. |
| Strong inducer of CYP3A4/P-gp (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin)   | CT                 | Concomitant use of NERLYNX with a strong CYP3A4/P-gp inducer (rifampin) reduced neratinib $C_{max}$ by 76% and AUC by 87%.   | Avoid concomitant use of NERLYNX with strong CYP3A4 and/or P-gp inducers.     |
| Antacids   | T                  | Drugs that alter the pH of the upper GI tract, may alter the solubility of neratinib and hence its bioavailability.  | Separate dosing of NERLYNX and antacids by 3 hours.                           |
| Proton Pump Inhibitor  | CT                 | In a trial of 15 healthy subjects, administration of a single 240 mg dose of NERLYNX combined with a 30 mg lansoprazole dose at steady state decreased neratinib $C_{max}$ and AUC by 71% and 65%, respectively. | Avoid concomitant use.  |



|  |    |   |  |
|--|----|---|--|
| H <sub>2</sub> -receptor antagonist  | CT | When NERLYNX was administered 2 hours following a 300 mg dose of an H <sub>2</sub> -receptor antagonist (ranitidine), the neratinib C <sub>max</sub> and AUC were reduced by 55% and 47%, respectively. When NERLYNX was administered 2 hours prior to ranitidine 150 mg twice daily (administered in the morning and evening, approximately 12 hours apart), the neratinib C <sub>max</sub> and AUC were reduced by 40% and 30%, respectively. | Avoid concomitant use. If short-term use of a H <sub>2</sub> -receptor antagonist cannot be avoided, NERLYNX must be taken at least 2 hours before the morning dose and 10 hours after the evening dose of the H <sub>2</sub> -receptor antagonist dosing. |
| <b>Pharmacokinetic Interactions (Drugs that may have their plasma concentrations altered by NERLYNX)</b> |    |   |  |
| P-glycoprotein substrate (e.g., digoxin, dabigatran, fexofenadine)                                       | CT | 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 <sub>max</sub> by 54% and AUC by 32%.  | Caution is warranted and therapeutic concentration monitoring of P-gp substrates with a narrow therapeutic index is recommended.   |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### 8.3 Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase neratinib plasma concentrations and should be avoided.

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<sub>max</sub> and AUC<sub>inf</sub> 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<sub>max</sub> and AUC<sub>inf</sub> by 1.2-fold (90% CI: 0.97- 1.42) and 1.1-fold (90% CI: 1.02- 1.24), respectively.

### 8.4 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4 that may decrease neratinib plasma concentrations and should be avoided.

## 9 ACTION AND CLINICAL PHARMACOLOGY

### 9.1 Mechanism of Action

Neratinib is a protein 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.

### 9.2 Pharmacodynamics

#### Cardiac Electrophysiology

The effects of NERLYNX on ECG interval parameters were evaluated in a randomized, placebo- and positive-controlled, double-blind, single-dose, crossover study in 60 healthy subjects. The study was conducted in two parts. Part A was a three-way crossover of single dose treatment with test article (neratinib 240 mg, placebo, or moxifloxacin 400 mg) in a fed state. Part B was a two-way crossover of a single dose of test article (neratinib 240 mg or placebo) co-administered with ketoconazole 400 mg/day in a fasting state. Ketoconazole 400 mg was administered for four days, beginning one day prior to neratinib administration.

Following single dose treatment with neratinib 240 mg, in the presence and absence of the CYP3A inhibitor, ketoconazole 400 mg/day, no clinically relevant effects on the QTc interval, the QRS duration, the PR interval, or ventricular heart rate were observed. The mean (SD)  $C_{max}$  of single dose neratinib 240 mg was 68.0 (27.0) ng/mL when administered alone and 162.6 (75.0) ng/mL when administered with ketoconazole 400 mg/day.

### 9.3 Pharmacokinetics

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

Table 9 summarizes the single dose PK parameters in healthy subjects under fed and fasted conditions.

**Table 9. Summary of Pharmacokinetics (PK) Parameters of NERLYNX Following Single Ascending Oral Doses of 240 mg of NERLYNX to Healthy Subjects under Fasted and Fed Conditions : Arithmetic Mean (+SD).**

|                        |                   | $C_{max}$<br>(ng/mL) | $T_{max}$<br>(hr) | $t_{1/2}$<br>(h) | $AUC_{0-\infty}$<br>(ng.h/mL) | CL<br>(L/hr/kg) | Vd<br>(L/kg)    |
|------------------------|-------------------|----------------------|-------------------|------------------|-------------------------------|-----------------|-----------------|
| Single<br>dose<br>mean | Fed<br>(high fat) | 74.4<br>(20.87)      | 6                 | 11<br>(1.84)     | 1357<br>(386)                 | 2.62<br>(0.66)  | 40.8<br>(7.86)  |
|                        | Fasted            | 44.6<br>(15.0)       | 4                 | 9.8<br>(2.97)    | 667<br>(268)                  | 6.27<br>(4.63)  | 78.6<br>(36.39) |

$C_{max}$  = maximum (peak) concentration;  $T_{max}$  = median time at peak concentration;

$T_{1/2}$  = half-life; AUC = total area under the time-concentration curve; CL/F = apparent clearance; Vd = apparent volume of distribution

**Absorption:** Following oral single-dose administration, neratinib showed a moderate rate of absorption with a median  $T_{max}$  after approximately 6 hours under fed conditions versus 4 hours under fasted conditions.

A preliminary food-effect assessment was conducted in healthy subjects 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.

**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 was bound predominantly to human serum albumin and human alpha-1 acid glycoprotein.

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

Following oral administration of NERLYNX, neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of NERLYNX in healthy subjects (N=25), the systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11 were 15%, 33%, 22% and 4% of the systemic neratinib exposure (AUC), respectively.

**Elimination and Excretion:** The mean apparent oral clearance (CL/F) of neratinib was high and variable (ranging from 159 L/kg to 456 L/kg (2.0 to 6.3 L/h/kg)), relatively similar at all dosages, and similar in healthy volunteers and cancer patients. Following single doses of neratinib, the mean apparent plasma half-life of neratinib was 17 hours in patients.

In a mass balance analysis in healthy subjects, after oral administration of 200 mg NERLYNX, fecal excretion accounted for approximately 97.1% and urinary excretion accounted for 1.13% of the total dose. The excretion was rapid and complete with the majority of the radioactivity (61%) recovered within 96 hours and 98% recovered after 10 days.

### Special Populations and Conditions

**Pediatrics:** Pharmacokinetic studies of neratinib have not been evaluated in children under 18 years of age.

**Geriatrics:** Age (range, 28-90 years of age) has no clinically significant effect on neratinib pharmacokinetics in patients with cancer based on a population PK analysis.

**Gender:** Population pharmacokinetic analyses showed that sex had no clinically meaningful effect on the pharmacokinetics of neratinib.

**Ethnic Origin:** Based on a population PK analysis, race does not have a clinically significant effect on neratinib pharmacokinetics.

**Hepatic Insufficiency:** 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

with Child-Pugh Class A, B and C) and in healthy subjects (N=9) with normal hepatic function. Neratinib exposures in patients with Child-Pugh Class A (mild impairment) and B (moderate impairment) were similar to that in normal healthy volunteers. In patients with severe hepatic impairment (Child-Pugh Class C),  $C_{max}$  and AUC increased by 273% and 281%, respectively, as compared to healthy control subjects.

**Renal Impairment:** In a population pharmacokinetic analysis, NERLYNX clearance among 593 subjects (393 patients and 200 healthy volunteers) showed no relationship with renal function measured as creatinine clearance, which ranged from 30.6 to 213 mL/min/1.73m<sup>2</sup> in the analysis population. The population included 179 subjects with mild renal impairment (30 to < 60 mL/min/1.73m<sup>2</sup>) and 37 subjects with moderate renal impairment (60 to < 90 mL/min/1.73m<sup>2</sup>). NERLYNX has not been studied in patients with severe renal impairment (< 30 mL/min/1.73m<sup>2</sup>).

There have been no dedicated pharmacokinetic studies in patients with renal impairment or those undergoing hemodialysis.

## **10 STORAGE, STABILITY AND DISPOSAL**

Store at: 15 to 25 °C. Keep bottle tightly closed.

Store in the original package in order to protect from moisture.

Keep in a safe place out of reach and sight of children.

## **11 SPECIAL HANDLING INSTRUCTIONS**

Any unused product or waste material should be disposed in accordance with local requirements.

## PART II: SCIENTIFIC INFORMATION

### 12 PHARMACEUTICAL INFORMATION

#### Drug Substance

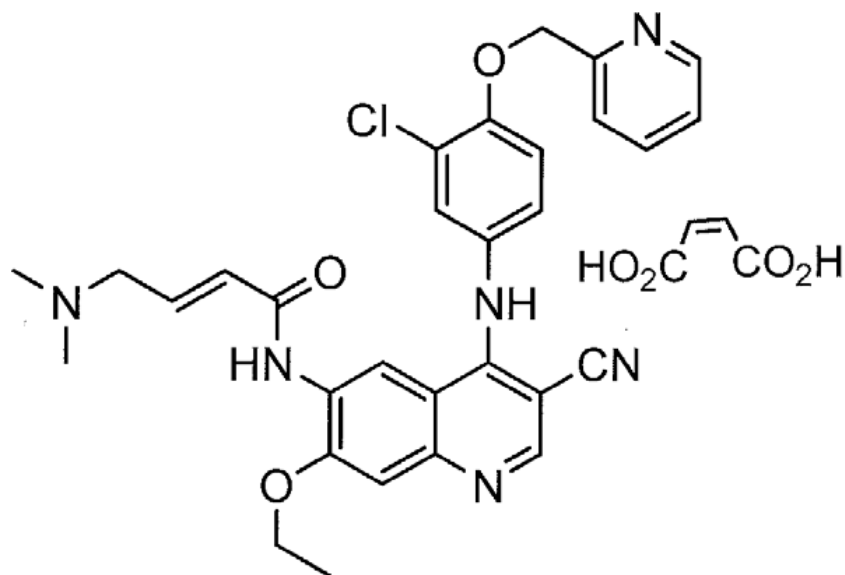
Proper name/Common Name: Neratinib maleate

Chemical name: (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate

Molecular formula:  $C_{30}H_{29}ClN_6O_3 \cdot C_4H_4O_4$

Molecular mass: 673.11

Structural formula:



Physicochemical properties:

Neratinib maleate is an off-white to yellow powder with a melting temperature of approximately 201°C, followed immediately by decomposition. The solubility of neratinib maleate increases dramatically in acidic pH. The maximum aqueous solubility of neratinib maleate is 32.90 mg/mL at pH 1.2 and becomes negligible (0.08 mg/mL or less) at approximately pH 5.0 and above.

## 13 CLINICAL TRIALS

The safety and efficacy of NERLYNX were investigated in a multicenter, randomized, double blind, placebo-controlled study in women with early-stage HER2-positive breast cancer, who had previously received trastuzumab-based adjuvant therapy (ExteNET).

### 13.1 Trial Design and Study Demographics

A total of 2840 women with early-stage HER2-positive breast cancer were 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 prior trastuzumab was given sequentially versus concurrently with chemotherapy. NERLYNX 240 mg or placebo was given orally once daily for one year. The median duration of treatment was 11.6 months in the NERLYNX arm vs. 11.8 months in the placebo arm. Patients who were hormone receptor-positive (defined as ER-positive and/or PgR-positive) received concomitant endocrine therapy.

Patient demographics and disease characteristics were balanced between treatment arms (see Table 10). Overall, patients had a median age of 52 years (range 23 to 83); 12% of patients were 65 years of age or older. The majority of patients were Caucasian (81%), and most (92%) had an ECOG performance status of 0. Fifty-seven percent (57%) had hormone receptor positive disease. At initial diagnosis, 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, 31% had Stage III disease and 18% of unknown stage. Median time from diagnosis to randomization was 22.1 months.

Twenty-five percent (25%) of patients had received prior neoadjuvant therapy and 17% initiated trastuzumab in the neoadjuvant setting. The majority of patients (81%) were enrolled within one year of completion of trastuzumab-based adjuvant treatment. Median time from the last adjuvant trastuzumab treatment to randomization was 4.4 months in the NERLYNX arm vs. 4.6 months in the placebo arm.

**Table 10. Summary of Patient Demographics and Disease Characteristics in ExteNET**

|   | <b>NERLYNX<br/>(n = 1420)</b> | <b>Placebo<br/>(n = 1420)</b> |
|---|-------------------------------|-------------------------------|
| <b>Age, Median (Range)</b>                    | 52.0 (25.0, 83.0)             | 52.0 (23.0, 82.0)             |
| <b>Race – n (%)</b>                           |                               |                               |
| Asian   | 188 (13.2)                    | 197 (13.9)                    |
| Black or African American                     | 27 (1.9)                      | 47 (3.3)                      |
| White   | 1165 (82.0)                   | 1135 (79.9)                   |
| Other   | 40 (2.8)                      | 41 (2.9)                      |
| <b>Body Weight (kg), Mean (SD)</b>            | 72.51 (16.29)                 | 72.64 (16.41)                 |
| <b>Menopausal Status at Diagnosis – n (%)</b> |                               |                               |
| Premenopausal                                 | 663 (46.7)                    | 664 (46.8)                    |
| Postmenopausal                                | 757 (53.3)                    | 756 (53.2)                    |
| <b>Disease Stage at Diagnosis – n (%)</b>     |                               |                               |
| I   | 139 (9.8)                     | 152 (10.7)                    |

|   | <b>NERLYNX<br/>(n = 1420)</b> | <b>Placebo<br/>(n = 1420)</b> |
|---|-------------------------------|-------------------------------|
| IIA   | 328 (23.1)                    | 306 (21.5)                    |
| IIB   | 268 (18.9)                    | 258 (18.2)                    |
| IIIA  | 273 (19.2)                    | 260 (18.3)                    |
| IIIB  | 27 (1.9)                      | 24 (1.7)                      |
| IIIC  | 144 (10.1)                    | 146 (10.3)                    |
| Unknown   | 241 (17.0)                    | 274 (19.3)                    |
| <b>Time from Diagnosis to<br/>Randomization (Month),<br/>Median (Range)</b> | 21.8 (7.7 – 73.7)             | 22.3 (7.8 – 103)              |
| <b>ECOG Performance Status – n (%)</b>                                      |                               |                               |
| 0   | 1317 (92.7)                   | 1303 (91.8)                   |
| 1   | 98 (6.9)                      | 114 (8.0)                     |
| Unknown   | 5 (0.4)                       | 3 (0.2)                       |
| <b>Hormone Receptor Status – n (%)</b>                                      |                               |                               |
| Positive  | 816 (57.5)                    | 815 (57.4)                    |
| Negative  | 604 (42.5)                    | 605 (42.6)                    |
| <b>Nodal Status – n (%)</b>   |                               |                               |
| Negative  | 335 (23.6)                    | 336 (23.7)                    |
| 1-3 Positive Nodes  | 664 (46.8)                    | 664 (46.8)                    |
| ≥ 4 Positive Nodes  | 421 (29.6)                    | 420 (29.6)                    |
| <b>Prior Trastuzumab and Chemotherapy – n (%)</b>                           |                               |                               |
| Concurrent  | 884 (62.3)                    | 886 (62.4)                    |
| Sequential  | 536 (37.7)                    | 534 (37.6)                    |
| <b>Time from Completion of Trastuzumab</b>                                  |                               |                               |
| ≤ 1 year  | 1152 (81.1)                   | 1145 (80.6)                   |
| > 1 year  | 268 (18.9)                    | 275 (19.4)                    |

## 13.2 Study Results

The primary efficacy outcome measure was invasive disease-free survival (iDFS) at 24 months defined as the time from randomization to the first occurrence of invasive tumor recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause. Secondary endpoints of the study were disease-free survival including ductal carcinoma *in situ* (DFS-DCIS), distant disease-free survival (DDFS), time to distant recurrence (TTDR), and cumulative incidence of central nervous system (CNS) recurrences.

The primary analysis of the efficacy results of the ITT population from the ExteNET study is summarized in [Table 11](#) and a Kaplan-Meier (K-M) plot in [Figure 1](#). The primary analysis demonstrated that NERLYNX significantly reduced the risk of invasive disease recurrence or death at 24 months by 34% (HR=0.66 with 95% CI: 0.49, 0.90, two-sided p = 0.008) when compared to placebo in the ITT population.

Based on the primary analyses of the secondary endpoints, NERLYNX reduced the risk of DFS-DCIS events by 39% compared to the placebo. A trending benefit was shown for DDFS and TTDR in patients treated with NERLYNX (Table 11). The most frequent site for distance recurrence as DDFS events in NERLYNX-treated patients was bone, followed by liver and brain.

**Table 11. Primary Efficacy Analyses at 24 Months – ITT Population**

| Endpoint   | Patient with events (%) |                  | Estimated 2 year event free rates <sup>1</sup> (%) |                  | Hazard ratio (95% CI) <sup>2</sup> | P-value <sup>3</sup> |
|--|-------------------------|------------------|--|------------------|------------------------------------|----------------------|
|  | NERLYNX (N=1420)        | Placebo (N=1420) | NERLYNX (N=1420)                                   | Placebo (N=1420) |                                    |                      |
| Invasive disease-free survival (iDFS)                                      | 4.7                     | 7.5              | 94.2   | 91.9             | 0.66 (0.49, 0.90)                  | 0.008                |
| Disease-free survival including ductal carcinoma <i>in situ</i> (DFS-DCIS) | 4.7                     | 8                | 94.2   | 91.3             | 0.61 (0.45, 0.83)                  | 0.001                |
| Distant disease-free survival (DDFS)                                       | 3.8                     | 5.4              | 95.3   | 94.0             | 0.74 (0.52, 1.05)                  | 0.094                |
| Time to distant recurrence (TTDR)  | 3.7                     | 5.3              | 95.5   | 94.2             | 0.73 (0.51, 1.04)                  | 0.087                |
| Cumulative incidence of CNS recurrence                                     | 0.8                     | 1.1              | 0.92   | 1.16             | –                                  | 0.548                |

CNS = central nervous system.

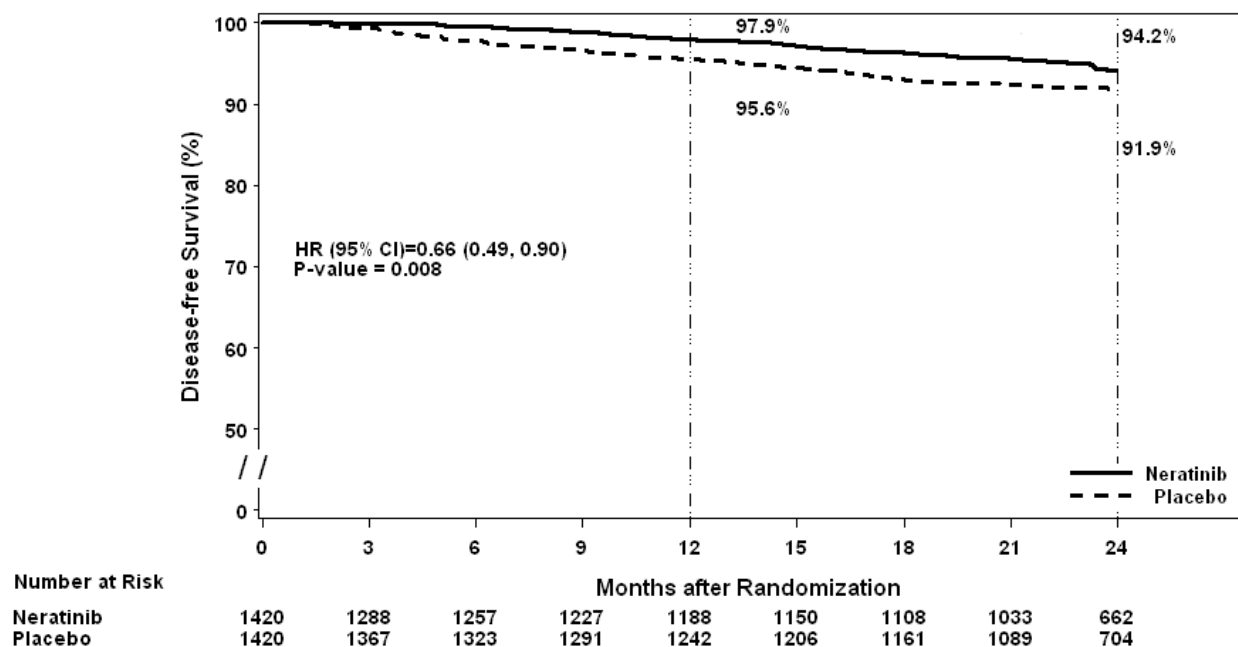
<sup>1</sup> Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

<sup>2</sup> Stratified by prior trastuzumab (concurrent vs. sequential), nodal status (0-3 positive nodes vs. ≥4 positive nodes), and ER/PR status (positive vs. negative).

<sup>3</sup> Stratified 2-sided log-rank test.



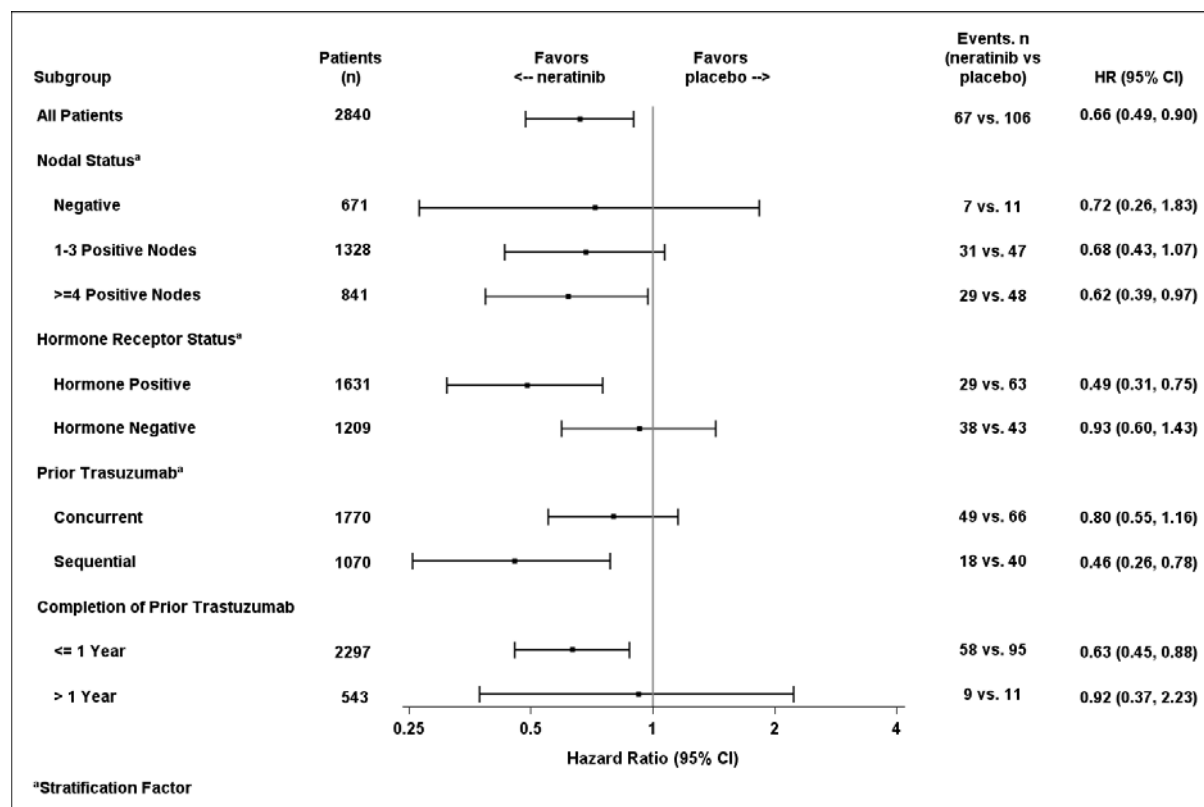
**Figure 1. Kaplan-Meier iDFS Estimates Primary Analysis at 24 Months – ITT Population**



The pre-specified subgroup analyses were performed for the three stratification factors used in randomization (HRc positive vs. HRc negative; nodal disease, prior trastuzumab given sequentially vs. concurrently with chemotherapy), and time from completion of trastuzumab ( $\leq 1$  vs.  $> 1$  year).

A Forest plot of the subgroup analyses of iDFS for the ITT population is shown in [Figure 2](#). In most subgroups analyzed, the treatment effect was in favor of NERLYNX. However, efficacy of NERLYNX (versus placebo) was not demonstrated in patients who were hormone receptor negative ( $n = 604$  and  $605$ , respectively); the hazard ratio for iDFS at 24 months was  $0.93$  (95% CI:  $0.60, 1.43$ ,  $p = 0.365$ ). Efficacy of NERLYNX (versus placebo) was also not significantly different in patients who were randomized over one year after completion of trastuzumab-based adjuvant therapy ( $n = 268$  and  $275$ , respectively). The hazard ratio for iDFS at 24 months was  $0.92$  (95% CI:  $0.37, 2.23$ ,  $p = 0.430$ ) in this population.

**Figure 2: Forest Plot of Subgroup Analyses of iDFS – ITT population**



In an exploratory subgroup analysis for patients who were hormone receptor-positive and less than one year from completion of trastuzumab-based adjuvant therapy, the hazard ratio for invasive disease-free survival was 0.49 (95%CI: 0.30, 0.78). The estimated 2-year event-free rate was 95.3% for NERLYNX arm and 90.8% for placebo arm with a rate difference of 4.5%.

Approximately 75% of the ITT population was re-consented for 5-year follow-up. 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.

## 14 NON-CLINICAL TOXICOLOGY

### General Toxicology

#### *Repeated-Dose Studies*

##### **Rat**

Neratinib was administered orally at doses of 3, 10, and 30 mg/kg/day to rats for 26 weeks. Neratinib-related effects were observed in the liver (hepatic biliary epithelial cell vacuolation) and skin (inflammation) at 30 mg/kg/day, in the intestinal tract (luminal dilatation of the duodenum and ileum, mixed cell inflammation and crypt abscess of the cecum, villous atrophy of the ileum, mixed cell inflammation of the colon) at doses of ≥10 mg/kg/day, and in the mammary gland (atrophy) in males and lymph nodes (plasmacytosis, sinus histiocytosis) at

doses of  $\geq 3$  mg/kg/day. Complete or partial recovery was observed for all target organs after a 28-day recovery period. The dose of 3 mg/kg/day in rats was approximately 5 times the maximum recommended human dose of 240 mg/day based on AUC comparison.

### **Dog**

Neratinib was administered orally to male and female beagle dogs for at least 39 consecutive weeks at dose levels of 0.5, 2, or 6 mg/kg/day (up to 0.8 times the AUC in patients receiving the recommended dose of 240 mg/day). Neratinib-related microscopic changes were observed in the duodenal papilla (histiocytosis) at 6 mg/kg/day, and in the gall bladder (mucinous hyperplasia, lymphohistiocytic inflammation), mesenteric lymph nodes (sinus erythrocytosis), and testes (tubular hyperplasia) at doses of  $\geq 0.5$  mg/kg/day. The dose of 0.5 mg/kg/day in dogs was approximately 0.05 times the maximum recommended human dose of 240 mg/day based on AUC comparison.

### **Carcinogenicity**

Neratinib was not carcinogenic in a 6-month Tg.rasH2 transgenic mouse study at oral doses of up to 50 mg/kg/day in males and 125 mg/kg/day in females (approximately 10-33 times the AUC in patients receiving the recommended dose of 240 mg/day). Similarly, neratinib was not carcinogenic in a 2-year rat study at oral doses up to 10 mg/kg/day (approximately 22-35 times the AUC in patients receiving the recommended dose of 240 mg).

### **Mutagenicity**

Neratinib and its metabolites M3, M6, M7 and M11 were not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay. Neratinib and M3 were not clastogenic in an *in vivo* rat bone marrow micronucleus assay.

## **Reproductive and Developmental Toxicology**

### ***Impairment of Fertility***

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<sup>2</sup> basis) to either males or females 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  $\geq 0.5$  mg/kg/day. This finding was observed at AUCs that were approximately 0.05 times the AUC in patients at the maximum recommended dose of 240 mg.

### ***Developmental Toxicity***

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<sup>2</sup> 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  $\geq 6$  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  $\geq 3$  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  $\geq 10$  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 of  $\geq 5$  mg/kg/day (approximately 0.2 times the maximum recommended dose of 240 mg/day in patients on a  $mg/m^2$  basis).

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

Pr **NERLYNX**<sup>®</sup>  
neratinib tablets

Read this carefully before you start taking NERLYNX and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NERLYNX.

**What is NERLYNX used for?**

NERLYNX is used to treat women who have early-stage breast cancer, when:

- the cancer cells produce a larger amount of HER2 proteins; and
- the cancer cells are sensitive to female hormones.

To receive NERLYNX you will have had previous treatment with the medicine trastuzumab within the last 12 months.

Tests are used to find out if your cancer cells produce large amounts of HER2 proteins and are hormone-sensitive.

**How does NERLYNX work?**

NERLYNX is a kinase inhibitor, which interferes with the growth of certain tumor cells.

**What are the ingredients in NERLYNX?**

Medicinal ingredients: neratinib (as neratinib maleate)

Non-medicinal ingredients: colloidal silicon dioxide, crospovidone, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, purified water, talc, titanium dioxide.

**NERLYNX comes in the following dosage forms:**

Tablets, 40 mg

**Do not use NERLYNX if you:**

- are allergic to neratinib or any of the other ingredients in this medicine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NERLYNX. Talk about any health conditions or problems you may have, including if you:**

- have a liver condition
- have a heart condition
- are younger than 18 years of age. The effects of NERLYNX in people younger than 18 years old are not known.

**Other warnings you should know about:**

Female patients:

- Avoid becoming pregnant while taking NERLYNX. It may harm your unborn baby or

make you lose the pregnancy.

- Use two forms of birth control while you are taking NERLYNX. Keep using these forms of birth control for 1 month after your last dose of NERLYNX.
- Talk to your healthcare professional about birth control methods that may be right for you.
- If you do become pregnant, or think you are pregnant during your treatment with NERLYNX, tell your healthcare professional right away.
- **For women who can get pregnant:** a pregnancy test should be done before you start to take NERLYNX.
- Do not breastfeed while you are taking NERLYNX and for one month after your last dose. It is not known if NERLYNX passes into your breast milk. You and your healthcare professional should decide if you will take NERLYNX or breastfeed.

Male patients:

- Avoid fathering a child while taking NERLYNX.
- Use effective birth control when having sexual intercourse with a female partner who is able to get pregnant. Use these birth control methods while you are taking NERLYNX and for 3 months after your last dose.
- If your partner gets pregnant, tell your healthcare professional right away.

Diarrhea:

Diarrhea (2 or more loose or liquid bowel movements in a day) is a common side effect of taking NERLYNX. It can be severe and cause you to be **dehydrated**, have low blood pressure or **kidney problems**. Your healthcare professional should prescribe another medicine to take with your first dose of NERLYNX. This medicine will help prevent diarrhea. You should continue to take this medicine for the first two months of your treatment with NERLYNX. Your healthcare professional will monitor you for severe diarrhea.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

Some medicines can affect the level of NERLYNX in your body. NERLYNX can also affect the way some other medicines work. When medicines interact with NERLYNX, you may have more side effects. The medicines listed here may not be the only ones that could interact with NERLYNX.

**The following may interact with NERLYNX:**

- Medicines to lower stomach acid or treat stomach ulcers, such as:
  - medicines called proton pump inhibitors (like lansoprazole),
  - antacids (magnesium-aluminum-hydroxide), or
  - H<sub>2</sub>-receptor antagonists (like ranitidine and cimetidine).
- Ketoconazole, itraconazole, fluconazole, posaconazole, voriconazole - used to treat fungal infections.
- Clarithromycin, erythromycin, troleandomycin, ciprofloxacin, rifampin - used to treat bacterial infections.
- Medicines used to boost the effects of other medicines including, ritonavir, lopinavir, nelfinavir, indinavir, saquinavir, tipranavir, cobicistat, boceprevir - used to treat viral infections, including HIV.
- Phenytoin, carbamazepine - used to treat fits (seizures) and epilepsy.
- St John's Wort (*Hypericum perforatum*) - an herbal medicine used mainly for depression.

- Digoxin - used for heart problems.
- Diltiazem, verapamil, dronedarone – used to treat heart conditions or high blood pressure.
- Cimetidine – used to treat stomach problems.
- Idelalisib, crizotinib, imatinib, enzalutamide, mitotane – used to treat other types of cancer.
- Conivaptan – used to treat low sodium levels in blood.
- Dabigatran – used to prevent blot clots.
- Fexofenadine – used to treat symptoms of allergy.
- Nefazodone, fluvoxamine – used to treat depression.
- Tofisopam – used to treat anxiety.
- Aprepitant – used to treat nausea.
- Clotrimazole – used to treat yeast infections.
- Cyclosporine – used after organ transplantation.

Do not eat or drink any products or juices that contain grapefruit, grapefruit extract. These can affect the way NERLYNX works.

**How to take NERLYNX:**

- Take exactly as your healthcare professional tells you.
- Take once per day with food.
- Take at about the same time each day.
- Swallow tablets whole with a glass of water.
- Do NOT chew, crush or split tablets.

**Usual adult dose:** 240 mg (six tablets) once a day.

You may take NERYLYX for up to one year.

Your healthcare professional may change your dose of NERLYNX, stop your treatment for a short time or stop NERLYNX completely. This will be based on how you are feeling.

**Overdose:**

If you think you have taken too much NERLYNX, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose, take your next NERLYNX dose at the next scheduled time. Do not take extra tablets to make up the missed dose.

**What are possible side effects from using NERLYNX?**

These are not all the possible side effects you may feel when taking **NERLYNX**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of NERLYNX may include:

- fever
- chills
- nausea

- abdominal pain
- swelling of your abdomen
- upset stomach
- heartburn
- dry or inflamed mouth, or mouth sores
- gas
- hemorrhoids
- loss of appetite
- weight loss
- feeling tired or weak
- muscle spasms
- rash
- acne
- nail problems including color change or breakage
- dry skin
- nosebleeds
- runny nose
- nose dryness
- urinary tract infection
- pain or difficulty when urinating

NERLYNX may affect how your liver works. Blood tests will be done before you begin treatment, every month for the first 3 months, and then every 3 months as needed during your treatment with NERLYNX. The results of these tests will help your healthcare professional to check how well your liver is working.

If you experience any of the following signs or symptoms, call your healthcare professional right away. These may be signs that you are having liver problems.

- tiredness
- nausea
- vomiting
- pain in the right upper abdomen
- fever
- rash
- itching
- yellowing of your skin or whites of your eyes

Your healthcare professional will stop your treatment with NERLYNX if your blood tests show severe liver problems.

NERLYNX can also cause other abnormal blood test results. Your doctor will decide when to perform other blood tests and will interpret the results.



| <b>Serious side effects and what to do about them</b>  |                                      |              |   |
|--|--------------------------------------|--------------|---|
| Symptom / effect   | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|  | Only if severe                       | In all cases |   |
| <b>VERY COMMON</b><br><b>Diarrhea:</b> increased number of stools, loose or watery stools.   |                                      | X            |   |
| <b>Vomiting</b>  |                                      | X            |   |
| <b>COMMON</b><br><b>Dehydration</b> (loss of too much fluid from the body often due to nausea, vomiting and/or diarrhea, or not taking enough liquids by mouth): thirst, headache, loss of appetite, lack of sweating, decreased urine, low blood pressure, problems with kidney function. |                                      | X            |   |
| <b>Cellulitis or Erysipelas</b> (serious skin reactions): pain; tenderness; swelling; redness of the skin; painful red, raised patches on the skin, which may be warm to the touch; fever; chills; feeling unwell.   |                                      | X            |   |
| <b>Palmar-plantar erythrodysesthesia syndrome</b> (skin reaction also known as hand-foot syndrome): pain, tingling, swelling or redness, thick calluses and blisters on the palms of the hands or soles of the feet.   |                                      | X            |   |
| <b>Liver injury:</b> yellowing of the skin or the white of your eyes, dark or brown (tea colored) urine, nausea or vomiting, loss of appetite, feeling tired or weak.  |                                      | X            |   |
| <b>UNCOMMON</b><br><b>Cholelithiasis</b> (gallstones): intense pain in the upper abdomen, pain in right shoulder, nausea, vomiting.  |                                      | X            |   |
| <b>RARE</b><br><b>Kidney problems:</b> nausea, vomiting, fatigue, changes in how you urinate.  |                                      | X            |   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough

to interfere with your daily activities, talk to your healthcare professional.

### **Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### **Storage:**

- Store: 15 – 25°C in the original package to protect from moisture. Keep bottle tightly closed. Keep out of reach and sight of children.
- Do not take this medicine after the expiry date which is stated on the bottle after “EXP”. The expiry date refers to the last day of that month.
- Do not throw away any unused medicine in the garbage or down the drain or toilet. Ask your pharmacist how to best dispose of medicines that you no longer need. These measures will help to protect the environment.

### **If you want more information about NERLYNX:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada.html>), the manufacturer’s website (<https://www.gud-knight.com/>), by emailing [medinfo@gudknight.com](mailto:medinfo@gudknight.com), or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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