

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Nerlynx 40 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains neratinib maleate, equivalent to 40 mg neratinib.

For the full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Oval, red film-coated tablet with 'W104' debossed on one side. Tablet dimensions are 10.5 mm x 4.3 mm with thickness of 3.1 mm.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

### 4.2 Posology and method of administration

Nerlynx treatment should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

#### Posology

The recommended dose of Nerlynx is 240 mg (six 40 mg tablets) taken orally once daily, continuously for one year. Nerlynx should be taken with food, preferably in the morning. Patients should initiate treatment within 1 year after completion of trastuzumab 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 as shown in Table 2, Table 3, Table 4, and Table 5.

Discontinue Nerlynx for patients who:

- Fail to recover to Grade 0 to 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 1: 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 2: Nerlynx dose modifications and management – general toxicities\***

Severity of toxicity <sup>†</sup>	Action
Grade 3	Stop Nerlynx until recovery to Grade $\leq$ 1 or baseline within 3 weeks of stopping treatment. Then resume Nerlynx at the next lower dose level. If grade 3 toxicity does not recover within 3 weeks, discontinue Nerlynx permanently.
Grade 4	Discontinue Nerlynx permanently.

\* Refer to Table 3 and Table 4 below for management of diarrhoea and hepatotoxicity

<sup>†</sup> Per CTCAE v4.0

#### *Dose modifications for diarrhoea*

Diarrhoea management requires the correct use of an anti-diarrhoeal medicinal product, dietary changes, and appropriate dose modifications of Nerlynx. Guidelines for adjusting doses of Nerlynx in the setting of diarrhoea are shown in Table 3.

**Table 3: Dose modifications for diarrhoea**

Severity of diarrhoea*	Action
<ul style="list-style-type: none"> <li>Grade 1 diarrhoea [increase of &lt; 4 stools per day over baseline]</li> <li>Grade 2 diarrhoea [increase of 4-6 stools per day over baseline] lasting &lt; 5 days</li> <li>Grade 3 diarrhoea [increase of <math>\geq</math> 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting <math>\leq</math> 2 days</li> </ul>	<ul style="list-style-type: none"> <li>Adjust anti-diarrhoeal treatment</li> <li>Diet modifications</li> <li>Fluid intake of ~2 L should be maintained to avoid dehydration</li> <li>Once event resolves to <math>\leq</math> Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent Nerlynx administration (refer to section 4.4).</li> </ul>

Severity of diarrhoea*	Action
<ul style="list-style-type: none"> <li>Any grade with complicated features<sup>†</sup></li> <li>Grade 2 diarrhoea lasting 5 days or longer<sup>‡</sup></li> <li>Grade 3 diarrhoea lasting between 2 days and 3 weeks<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 diarrhoea resolves to Grade 0-1 in one week or less, then resume Nerlynx treatment at the same dose.</li> <li>If diarrhoea resolves to Grade 0-1 in longer than one week, then resume Nerlynx treatment at reduced dose (see Table 1).</li> <li>Once event resolves to ≤ Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent Nerlynx administration (refer to section 4.4).</li> <li>If grade 3 diarrhoea persists longer than 3weeks, discontinue Nerlynx permanently.</li> </ul>
<ul style="list-style-type: none"> <li>Grade 4 diarrhoea [life-threatening consequences; urgent intervention indicated]</li> </ul>	<ul style="list-style-type: none"> <li>Permanently discontinue Nerlynx treatment</li> </ul>
<ul style="list-style-type: none"> <li>Diarrhoea 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

#### *Missed dose*

Missed doses should not be replaced and treatment should resume with the next scheduled daily dose (see Section 4.9).

#### *Use of CYP3A4/Pgp inhibitors*

If the inhibitor cannot be avoided, reduce Nerlynx dose to 40 mg (one 40 mg tablet) taken once daily with a strong CYP3A4/Pgp inhibitor. After discontinuation of a strong CYP3A4/Pgp inhibitor, resume previous dose of Nerlynx 240 mg (see Section 4.4 and Section 4.5).

#### *Patients with 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 including patients on dialysis. Treatment of patients with severe renal impairment or on dialysis is not recommended (see Section 5.2).

#### *Patients with hepatic impairment*

No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. Treatment of patients with Child Pugh C hepatic impairment is not recommended (see Section 5.2).

#### *Dose modifications for hepatotoxicity*

Guidelines for dose adjustment of Nerlynx in the event of liver toxicity are shown in Table 5. (see Section 4.4).

**Table 4: Dose modifications for hepatotoxicity**

Severity of hepatotoxicity*	Action
<ul style="list-style-type: none"> <li>• Grade 3 ALT (&gt;5-20 x ULN) OR</li> <li>• Grade 3 bilirubin (&gt;3-10 x ULN)</li> </ul>	<ul style="list-style-type: none"> <li>• Stop Nerlynx until recovery to ≤ Grade 1</li> <li>• Evaluate alternative causes</li> <li>• 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.</li> </ul>
<ul style="list-style-type: none"> <li>• Grade 4 ALT (&gt;20 x ULN) OR</li> <li>• Grade 4 bilirubin (&gt;10 x ULN)</li> </ul>	<ul style="list-style-type: none"> <li>• Permanently discontinue Nerlynx</li> <li>• Evaluate alternative causes</li> </ul>

ULN=Upper Limit Normal; ALT= Alanine Aminotransferase

\* Per CTCAE v4.0

#### *Elderly*

No dose adjustment is required. There is no data in patients ≥85 years of age.

#### *Paediatric population*

There is no relevant use of Nerlynx in the paediatric population in the indication breast cancer.

#### Method of administration

Nerlynx is for oral use. The tablets should be swallowed whole preferably with water and should not be crushed or dissolved, and should be taken with food, preferably in the morning (see Section 5.2).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

Co-administration with the following medical products that are strong inducers of the CYP3A4/Pgp isoform of cytochrome P450:

- carbamazepine, phenobarbital, phenytoin (antiepileptics)
- St John's wort (*Hypericum perforatum*) (herbal product)
- rifampin (antimycobacterial)

Co-administration with moderate CYP3A4/P-gp inhibitors:

- fluconazole (antifungal)
- diltiazem, verapamil (calcium-channel blockers)
- erythromycin (antibiotic)

Severe hepatic impairment (Child-Pugh C).

### **4.4 Special warnings and precautions for use**

#### Diarrhoea

Diarrhoea has been reported during treatment with Nerlynx (see Section 4.2 and Section 4.8). The diarrhoea may be severe and associated with dehydration.

Diarrhoea generally occurs early during the first or second week of treatment with Nerlynx and may be recurrent.

Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product with the first dose of Nerlynx, and maintain regular dosing of the anti-diarrhoeal medicinal product during the first 1-2 months of Nerlynx treatment, titrating to 1-2 bowel movements per day.

### Elderly

Elderly patients ( $\geq 65$  years of age) are at a higher risk of renal insufficiency and dehydration which may be a complication of diarrhoea and these patients should be carefully monitored.

### Patients with a significant chronic gastrointestinal disorder

Patients with a significant chronic gastrointestinal disorder with diarrhoea as a major symptom were not included in the pivotal study, and should be carefully monitored.

### Renal impairment

Patients with renal impairment are at a higher risk of complications of dehydration if they develop diarrhoea, and these patients should be carefully monitored (see Section 4.2).

### Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh C) there is a 2.8-fold increase of exposure to neratinib (see Section 5.2).

Hepatotoxicity has been reported in patients treated with Nerlynx. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin should be monitored at 1 week, then monthly for the first 3 months and every 6 weeks thereafter while on treatment or as clinically indicated (see Section 4.2).

Patients who experience  $\geq$  Grade 3 diarrhoea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, jaundice, 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.

### Left ventricular function

Left ventricular dysfunction has been associated with HER2 inhibition. Nerlynx has not been studied in patients with less than lower limit of normal left ventricular ejection fraction (LVEF) or with significant cardiac history. In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.

### Proton pump inhibitors, H<sub>2</sub>-receptor antagonists and antacids

Co-administration with proton pump inhibitors (PPIs) and H<sub>2</sub>-receptor antagonists are not recommended. If an antacid is taken, separate the dosing of Nerlynx and the antacid by at least 3 hours.

### Pregnancy

Neratinib may cause foetal harm when administered to pregnant women (see Section 4.6).

### Skin and subcutaneous tissue disorders

Nerlynx is associated with skin and subcutaneous tissue disorders. Patients with symptomatic skin and subcutaneous tissue disorders should be carefully monitored (see Section 4.8).

### Concomitant treatment with inhibitors of CYP3A4 and P-gp

Concomitant treatment with strong CYP3A4 and P-gp inhibitors should be avoided due to risk of increased exposure to neratinib (see Section 4.2 and Section 4.5).

Grapefruit juice should be avoided during treatment with Nerlynx (see Section 4.5).

## **4.5 Interaction with other medicinal products and other forms of interaction**

### Effects of other substances on neratinib

#### *CYP3A4/Pgp inhibitors*

Co-administration of a single oral dose of 240 mg of neratinib in the presence of ketoconazole (400 mg once daily for 5 days), a strong CYP3A4/Pgp inhibitor, increased neratinib systemic

exposure. The  $C_{max}$  of neratinib increased by 3.2 fold and AUC increased by 4.8 fold when co-administered with ketoconazole, compared with neratinib administered alone.

Concomitant use of strong CYP3A4/Pgp inhibitors (e.g. atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and voriconazole) should be avoided. Grapefruit or grapefruit juice may also increase neratinib plasma concentrations and should be avoided.

#### *Proton pump inhibitors, H2-receptor antagonists and antacids*

The solubility of neratinib is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided, as neratinib solubility and absorption may decrease. A single 240 mg dose of neratinib combined with lansoprazole decreased AUC by up to 70%. Co-administration with proton pump inhibitors (PPIs) and H2-receptor antagonists is not recommended. Separate dosing of Nerlynx and antacids by at least 3 hours.

#### *CYP3A4/Pgp inducers*

Following concomitant administration with repeated doses of 600 mg rifampin, a strong CYP3A4/Pgp inducer, neratinib exposures were significantly decreased with mean values that were 24% and 13% of reference values (neratinib administered alone) for  $C_{max}$  and AUC, respectively.

Concurrent use of neratinib with potent CYP3A4/Pgp inducers (e.g. phenytoin, carbamazepine, rifampin, phenobarbital or herbal preparations containing St John's Wort/*Hypericum perforatum*) should be avoided.

#### Effects of neratinib on other substances

##### *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 (see Section 4.6).

##### *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 transporters*

In *in-vitro* studies, neratinib is an inhibitor of P-glycoprotein (P-gp) substrates. In healthy subjects, digoxin increased  $C_{max}$  by 54% and AUC increased by 32% when co-administered with multiple oral doses of neratinib 240 mg compared with exposures of digoxin alone. The clearance values of digoxin were equivalent following digoxin and digoxin plus neratinib. It appeared that the inhibitory effect of neratinib was primarily on P-gp activity in the gastrointestinal tract as a result of pre-systemic inhibition. This pre-systemic interaction of neratinib with digoxin might be clinically relevant for P-gp substrates with a narrow therapeutic window (e.g. dabigatran, digoxin, and fexofenadine). Patients who are treated concomitantly with therapeutic agents whose metabolism involves P-gp substrates in the gastrointestinal tract should be monitored carefully.

## **4.6 Fertility, pregnancy and lactation**

### Women of childbearing potential/Contraception in females and males

Based on findings in animals, neratinib may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking Nerlynx and for up to 1 month after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Nerlynx and for 1 month after stopping treatment.

It is currently unknown whether neratinib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method.

Men should use a barrier method of contraception during treatment and for 3 months after stopping treatment.

#### Pregnancy

There are no data from the use of Nerlynx in pregnant women. Studies in animals have shown embryo-foetal lethality and foetal morphological anomalies (see Section 5.3). The potential risk for humans is unknown. Nerlynx should not be used during pregnancy unless the clinical condition of the woman requires treatment with neratinib.

If neratinib is used during pregnancy, or if the patient becomes pregnant while taking Nerlynx, the patient should be informed of the potential hazard to the foetus.

#### Breast-feeding

It is not known whether neratinib is excreted in human milk. A risk to the breast-fed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Nerlynx, taking into account the importance of Nerlynx to the mother and the benefit of breast-feeding to the child.

#### Fertility

No fertility studies in women or men have been conducted. No significant changes in fertility parameters in male and female rats were detected in dosing up to 12 mg/kg/day (see Section 5.3).

### **4.7 Effects on ability to drive and use machines**

Nerlynx has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, dehydration, and syncope have been reported as adverse reactions with neratinib. The clinical status of the patient should be considered when assessing the patient's ability to perform tasks that require judgment, motor, or cognitive skills.

### **4.8 Undesirable effects**

#### Summary of the safety profile

The most common adverse reactions of any grade were diarrhoea (93.6%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%), abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), abdominal pain upper (13.2%), stomatitis (11.2%), and muscle spasms (10.0%).

The most common Grade 3-4 adverse reactions were diarrhoea (Grade 3, 36.9% and Grade 4, 0.2%) and vomiting (Grade 3, 3.4% and Grade 4, 0.1%).

Adverse reactions reported as serious included diarrhoea (1.9%), vomiting (1.3%), dehydration (1.1%), nausea (0.5%), alanine aminotransferase increased (0.4%), aspartate aminotransferase increased (0.4%), abdominal pain (0.3%), fatigue (0.3%) and decreased appetite (0.2%).

#### Tabulated list of adverse reactions

The table below lists adverse reactions observed with neratinib based on the assessment of pooled data from 1,710 patients.



The MedDRA frequency convention and system organ class database has been utilised for the classification of frequency:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 5: Adverse drug reactions due to Nerlynx in monotherapy breast cancer studies**

System Organ Class	Frequency	Adverse Drug Reaction
<b>Infections and infestations</b>	Common	Urinary tract infection
<b>Metabolism and nutrition disorders</b>	Very Common	Decreased appetite
	Common	Dehydration
<b>Respiratory, thoracic and mediastinal disorders</b>	Common	Epistaxis
<b>Gastrointestinal disorders</b>	Very Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal pain upper, and stomatitis <sup>1</sup>
	Common	Abdominal distension, dry mouth and dyspepsia
<b>Hepatobiliary disorders</b>	Common	Alanine aminotransferase increased, and aspartate aminotransferase increased
	Uncommon	Blood bilirubin increased
<b>Skin and subcutaneous tissue disorders</b>	Very Common	Rash <sup>2</sup>
	Common	Nail disorder <sup>3</sup> , skin fissures and dry skin
<b>Musculoskeletal and connective tissue disorders</b>	Very Common	Muscle spasms
<b>Renal and urinary disorders</b>	Common	Blood creatinine increased
	Uncommon	Renal failure
<b>General disorders and administration site conditions</b>	Very common	Fatigue
<b>Investigations</b>	Common	Weight decreased

<sup>1</sup> Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, and mucosal inflammation.

<sup>2</sup> Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, and rash pustular.

<sup>3</sup> Includes nail disorder, paronychia, onychoclasia, and nail discolouration.

#### Description of selected adverse reactions

##### *Diarrhoea*

Of the 1,660 patients treated with Nerlynx monotherapy without loperamide prophylaxis, 94.6% experienced at least 1 episode of diarrhoea. Grade 3 diarrhoea was reported in 37.5% of Nerlynx patients. 0.2% of patients had diarrhoea classified as Grade 4. Diarrhoea led to hospitalisation in 1.9% of Nerlynx-treated patients.

Diarrhoea generally occurred in the first month, with 83.6% of patients reporting this toxicity in the first week, 46.9% in the second week, 40.2% in the third week and 43.2% in the fourth week (median time to first onset was 2 days).

The median duration of a single episode of any grade diarrhoea was 2 days. The median cumulative duration of any grade diarrhoea was 59 days and the median cumulative duration of Grade 3 diarrhoea was 5 days.

Diarrhoea was also the most common adverse reaction leading to discontinuation, 14.4 % of patients treated with Nerlynx without loperamide prophylaxis discontinued treatment due to diarrhoea. Dose reductions occurred in 24.7% of Nerlynx-treated patients.

#### *Rash*

In the Nerlynx monotherapy group, 16.7% of patients experienced rash. The incidence of Grade 1 and Grade 2 was 13.3% and 2.9% respectively; 0.4% of Nerlynx-treated patients experienced Grade 3 rash.

#### *Nail disorders*

In the Nerlynx monotherapy group, 7.8% patients experience nail disorders. The incidence of Grade 1 and Grade 2 was 6.2% and 1.4% respectively. There were 0.2% of Nerlynx treated patients who experienced Grade 3 nail disorder.

Both rash and nail disorders led to treatment discontinuation in 0.6% of Nerlynx-treated patients.

#### *Hepatotoxicity*

Hepatic-associated adverse reactions in the pivotal phase III study, ExteNET (3004), were reported more frequently in the Nerlynx arm compared to the placebo arm (12.4% vs. 6.6%), due primarily to alanine aminotransferase (ALT) increased (8.5% vs. 3.2%), aspartate aminotransferase (AST) increased (7.4 vs 3.3%) and blood alkaline phosphatase increased (2.1% vs. 1.1%). Grade 3 adverse reactions were reported in 1.6% vs 0.5% and Grade 4 adverse reactions were reported in 0.2% vs. 0.1%, Nerlynx- and placebo-treated patients, respectively. Grade 3 ALT increased was reported in 1.1% vs 0.2% and Grade 4 ALT increased was reported in 0.2% vs 0.0% of Nerlynx- vs placebo-treated patients. Grade 3 AST increased was reported in 0.5% vs 0.3% and Grade 4 AST increased was reported in 0.2% vs 0.0%, of Nerlynx- vs placebo-treated patients. There was no Grade 3 or 4 adverse reactions of blood bilirubin increased.

#### Other special populations

##### *Elderly*

In the pivotal phase III study, ExteNET (3004), the mean age was 52 years in the Nerlynx arm, 1236 patients were <65 years, 172 were ≥65 years, of whom 25 were 75 years or older.

There was a higher frequency of treatment discontinuations due to adverse reactions in the ≥65 years age group than <65 years age group; in the Nerlynx arm, the respective percentages were 44.8% compared with 25.2%, 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%), diarrhoea (1.7%), dehydration (1.2%), and renal failure (1.2%).

Treatment-emergent adverse reactions leading to hospitalisation in the Nerlynx arms versus the placebo arm was 6.3% vs 4.9% in the <65 years-old group and 8.7% vs. 8.1% in the ≥65 years-old group.

##### *Effect of race*

In the pivotal phase III study, ExteNET (3004), the frequency of Treatment Emergent Adverse Events (TEAEs) in the Skin and Subcutaneous Disorders System Organ Class (SOC) in Asian patients treated with Nerlynx was higher than in Caucasian patients (56.4% vs. 34.5%) but comparable in placebo patients (24.9% vs. 22.8%). Pooled safety data of 1710 patients treated with Nerlynx monotherapy showed a higher incidence of dermatologic toxicities in Asian patients (57.1%) versus Caucasian patients (34.6%).

In the analysis of pooled safety data, the majority of TEAEs in the Skin and Subcutaneous Disorders SOC in Asians were Grade 1 (43.3%) and Grade 2 (12.3%); in Caucasians, the incidence of Grade 1

and Grade 2 events was 25.6% and 7.8%, respectively. The frequency of Grade 3 events was similar between Asians and Caucasians (1.6% vs. 1.0%). There was no difference in frequency of SAEs in the Skin SOC between Asian and Caucasian subgroups. The most common TEAEs in the Skin SOC that occurred more frequently in Asian patients than in Caucasian patients were rash (29.4% vs. 13.5%), Palmar-plantar erythrodysesthesia syndrome (9.9% vs. 1.0%), and dermatitis acneiform (6.0 vs. 1.0%).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## **4.9 Overdose**

There is no specific antidote, and the benefit of haemodialysis 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, adverse reactions associated with overdose were most commonly diarrhoea, with or without nausea, vomiting and dehydration.

In a dose escalation study in healthy volunteers, single oral doses of Nerlynx up to 800 mg were administered. The frequency and severity of gastrointestinal disorders (diarrhoea, abdominal pain, nausea and vomiting) appeared to be dose-related. Single doses of Nerlynx greater than 800 mg have not been administered in the clinical studies.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE45

#### Mechanism of action

Neratinib is an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) that blocks mitogenic growth factor signal transduction through covalent, high affinity binding to the ATP binding site of 3 epidermal growth factor receptors (EGFRs): EGFR (encoded by ERBB1), HER2 (encoded by ERBB2), and HER4 (encoded by ERBB4) or their active heterodimers with HER3 (encoded by ERBB3). This results in sustained inhibition of these growth promoting pathways with HER2-amplified or over-expressed, or HER2-mutant breast cancers. Neratinib binds to the HER2 receptor, reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and potently inhibits tumour cell proliferation *in vitro*. Neratinib inhibited EGFR and/or HER2-expressing carcinoma cell lines with a cellular IC<sub>50</sub> <100 nM.

#### Clinical efficacy and safety

In the multicentre, randomised, double-blind, placebo-controlled, pivotal phase III study, ExteNET (3004), 2,840 women with early-stage HER2-positive breast cancer (as confirmed locally by assay) who had completed adjuvant treatment with trastuzumab were randomised 1:1 to receive either Nerlynx or placebo daily for one year. The median age in the intention-to-treat (ITT) population was 52.3 years (59.9% was ≥50 years old, 12.3% was ≥65 years old); 81.0% were Caucasian, 2.6% black or African American, 13.6% Asian and 2.9% other. At baseline, 57.4% had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 23.6% were node negative, 46.8% had one to three positive nodes and 29.6% had four or more positive nodes. Approximately 10% of patients had

Stage I tumours, approximately 40% had Stage II tumours and approximately 30% had Stage III tumours. Median time from the last adjuvant trastuzumab treatment to randomization was 4.5 months.

The primary endpoint of the study was invasive disease-free survival (iDFS). Secondary endpoints of the study included disease-free survival (DFS) including ductal carcinoma in situ (DFS-DCIS), time to distant recurrence (TTDR), distant disease-free survival (DDFS), cumulative incidence of central nervous system recurrence and overall survival (OS).

The primary analysis of the study after 2 years post-randomization demonstrated that Nerlynx significantly reduced the risk of invasive disease recurrence or death by 34% (HR=0.66 with 95% CI (0.49, 0.90), two-sided p = 0.008) in the ITT population.

**Table 6: Primary efficacy analyses – ITT and hormone receptor positive populations who are less than one year from completion of trastuzumab therapy**

Variable	Estimated 2 year event free rates <sup>1</sup> (%)		Hazard ratio (95% CI) <sup>2</sup>	P-value <sup>3</sup>
	<b>ITT population</b>			
	<b>Nerlynx (N=1420)</b>	<b>Placebo (N=1420)</b>		
Invasive disease-free survival	94.2	91.9	0.66 (0.49, 0.90)	0.008
Disease-free survival including ductal carcinoma <i>in situ</i>	94.2	91.3	0.61 (0.45, 0.83)	0.001
Distant disease-free survival	95.3	94.0	0.74 (0.52, 1.05)	0.094
Time to distant recurrence	95.5	94.2	0.73 (0.51, 1.04)	0.087
CNS recurrence	0.92	1.16	–	0.548
	<b>Hormone receptor positive population who are less than one year from completion of trastuzumab</b>			
	<b>Nerlynx (N=670)</b>	<b>Placebo (N=664)</b>	<b>Hazard ratio (95% CI)<sup>2</sup></b>	<b>P-value<sup>3</sup></b>
Invasive disease-free survival	95.3	90.8	0.49 (0.30, 0.78)	0.002
Disease-free survival including ductal carcinoma <i>in situ</i>	95.3	90.0	0.45 (0.28, 0.71)	<0.001
Distant disease-free survival	96.1	92.9	0.53 (0.31, 0.88)	0.015
Time to distant recurrence	96.3	93.3	0.53 (0.30, 0.89)	0.017
CNS recurrence	0.34	1.01	–	0.187

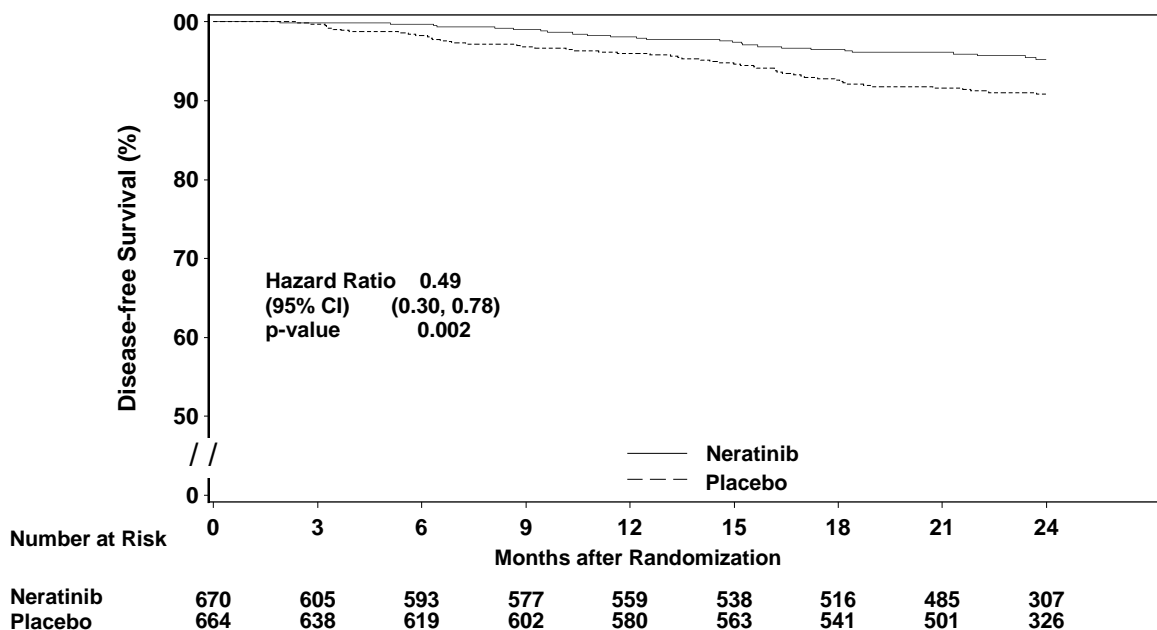
CNS = central nervous system.

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

<sup>2</sup> Unstratified Cox proportional hazards model

<sup>3</sup> Unstratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

**Figure 1: Kaplan-Meier plot of disease-free survival – hormone receptor positive population who are less than one year from completion of trastuzumab therapy**

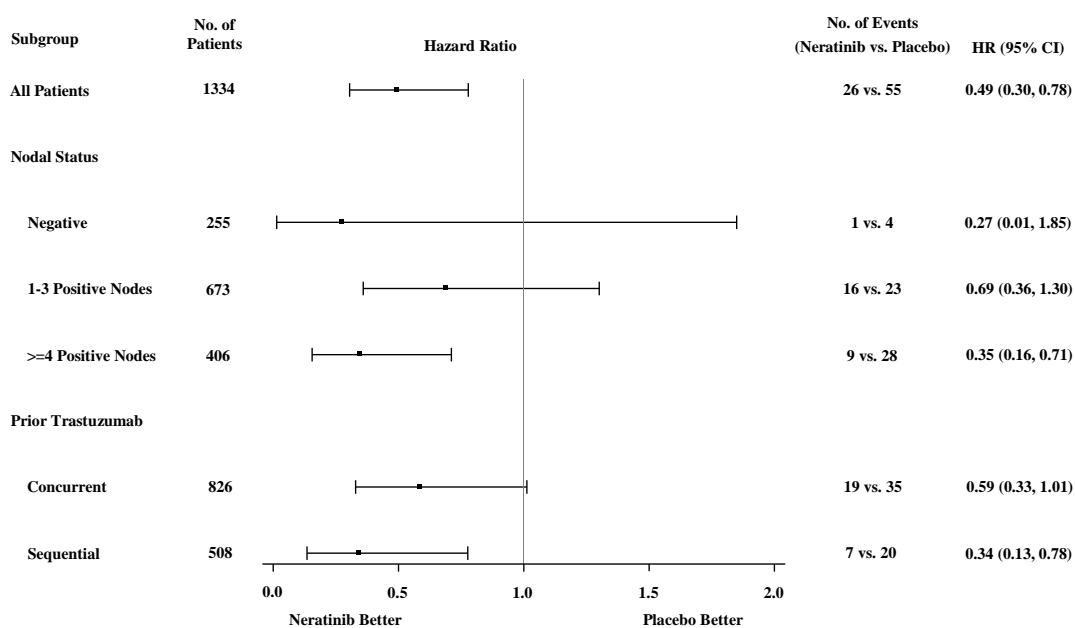


Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. While the treatment benefit of Nerlynx over placebo was maintained at five years, the effect size cannot be reliably estimated.

In patients that were hormone receptor negative, regardless of time from trastuzumab therapy, the hazard ratio for iDFS at 2 years was 0.93, with 95% CI (0.60, 1.43). In this population, efficacy has not been demonstrated.

For hormone receptor positive patients, the relative treatment benefit of Nerlynx within pre-specified patient subgroups is presented in Figure 2.

**Figure 2: Hormone receptor positive patients, disease-free survival by patient subgroup**



### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of breast carcinoma.

## **5.2 Pharmacokinetic properties**

The mass balance after administration of a single oral dose of 200 mg of neratinib was studied in six healthy subjects.

### Absorption

Following oral administration of 240 mg neratinib, absorption was slow and peak plasma concentrations of neratinib occurred around 7 hours after administration. A single dose of 240 mg neratinib taken with food increased  $C_{max}$  and AUC by approximately 17% and 23%, respectively, compared with administration in the fasting state. A single oral dose of 240 mg neratinib taken with a meal high in fat increased both  $C_{max}$  and AUC by approximately 100%.

### Distribution

Binding of neratinib to human plasma proteins, including covalent binding to human serum albumin (HSA), was greater than 98% and independent of concentration. Neratinib bound predominantly to HSA and human alpha-1 acid glycoprotein (AAG). *In vitro* studies demonstrated that neratinib is a substrate for P-glycoprotein (P-gp). Neratinib was not a potent inhibitor of human BSEP efflux transporter activity *in vitro*, with a reported  $IC_{50}$  value of  $> 10\mu M$ . Neratinib at  $10\mu M$  appeared to inhibit the BCRP efflux transporter. Neratinib produced no inhibitory activity towards the uptake transporters, OATP1B1\*1a, OATP1B3, OAT1, OAT3 and OCT2, with reported  $IC_{50}$  values were  $> 10\mu M$ . Neratinib produced inhibitory activity in OCT1 uptake transporter, with an  $IC_{50}$  of  $2.9\mu M$ .

### Biotransformation

Neratinib is metabolised primarily in liver microsomes by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

Preliminary metabolite profiling in human plasma indicates that after oral administration, neratinib undergoes oxidative metabolism through CYP3A4. Circulating metabolites include neratinib pyridine N-oxide (M3), N-desmethyl neratinib (M6), neratinib dimethylamine N-oxide (M7) and traces of hydroxyl neratinib N-oxide and neratinib bis-N-oxide (M11). Neratinib represents the most prominent component in plasma and systemic exposure to the metabolites (M3, M6, M7 and M11) after oral administration of neratinib is between 10% and 33% lower than parent in healthy subjects. The neratinib metabolites M3, M6, M7 and M11 were shown to have similar potencies to neratinib in either *in vitro* enzyme (binding assays) or cell based assays against cells expressing ERBB1, ERBB2 (HER2) and ERBB4.

#### Elimination

Following single doses of neratinib, the mean apparent plasma half-life of neratinib was 17 hours in patients.

#### Excretion of neratinib is primary via the faeces

Following the administration of a single radiolabelled dose of 200 mg neratinib oral solution, 97.1% and 1.1% of the administered dose was recovered in the faeces and urine, respectively. The excretion was rapid and complete, with the majority of the radioactivity (61%) recovered within 96 hours and 98% recovered after 10 days. It is not known if elimination is as unchanged drug or metabolites.

#### Pharmacokinetic/pharmacodynamic relationship(s)

##### *Renal impairment*

Pharmacokinetic studies in patients with renal impairment or undergoing dialysis have not been carried out. Population pharmacokinetic modelling revealed that creatinine clearance did not explain the variability between patients, hence, no dose modifications are recommended for patients with mild to moderate renal impairment.

##### *Hepatic impairment*

Neratinib is extensively metabolised in the liver. In subjects with severe pre-existing hepatic impairment (Child Pugh Class C) without cancer, the clearance of neratinib was decreased by 36% and exposure to neratinib increased by about 3-fold as compared to healthy volunteers.

### **5.3 Preclinical safety data**

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

#### Carcinogenesis, mutagenesis

Nerlynx was neither clastogenic nor mutagenic in the standard battery of genotoxicity studies.

Neratinib metabolites M3, M6, M7 and M11 are negative in the standard battery of *in vitro* genotoxicity studies.

A 6-month carcinogenicity study in Tg.rasH2 transgenic mice and the rat 2-year data showed no signs of carcinogenic potential.

#### Reproductive toxicity

In rabbits, there were no effects on mating or the ability of animals to become pregnant, but embryo-fetal lethality and foetal morphologic anomalies (e.g. domed head, dilation of brain ventricles and misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) were observed at doses that may be considered to be clinically relevant.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Mannitol (E421)

Microcrystalline cellulose

Crospovidone

Povidone

Silica, colloidal anhydrous

Magnesium stearate

#### Tablet coating

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol

Talc

Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

### **6.4 Special precautions for storage**

Keep the bottle tightly closed in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

### **6.5 Nature and contents of container**

White, 60 mL high density polyethylene (HDPE) round bottle with child-resistant, polypropylene closure, and foil induction inner seal.

An HDPE desiccant canister with 1 g silica gel is enclosed with the tablets in each bottle.

Each bottle contains 180 tablets.

### **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

Puma Biotechnology, Ltd.

11th Floor, Whitefriars, Lewins Mead

Bristol

BS1 2NT

United Kingdom



**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/18/1311/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

AndersonBrecon (UK) Limited  
Pharos House, Wye Valley Business Park  
Brecon Road  
Hay-on-Wye  
Hereford  
HR3 5PG  
UNITED KINGDOM

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Nerlynx in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Nerlynx is marketed, all healthcare professionals who are expected to prescribe/dispense Nerlynx, as well as all patients/carers who are expected to use Nerlynx, have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

**The physician educational material** should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient educational material
  - **The Guide for healthcare professionals** shall contain the following key elements:
- Name of the product, active substance and approved indication of the product
- Relevant information on the safety concern “Gastrointestinal toxicity (diarrhea)” (e.g. seriousness, severity, frequency, time to onset, duration, reversibility of the AE as applicable)
- Details of the population at higher risk for the safety concern
- Key message to convey in patients counselling on how to prevent and minimise Gastrointestinal toxicity through appropriate monitoring and management:
  - prophylactic treatment with antidiarrheal medicinal product
  - dietary changes
  - dose modification (with guideline to adjust doses)/ discontinuation of treatment
- The importance of handing over the educational material to the patients/carers at the end of counselling
- Remarks on the importance of reporting ADRs
  - **The patient educational material:**

The patient information pack should contain:

- Patient information leaflet
- A patient/carer treatment guide
- “My Treatment Journal”

**The Patient/carer guide** shall contain the following key messages (in lay language)

- Name of the product, active substance and approved indication of the product
- Relevant information of Gastrointestinal toxicity (diarrhea) (e.g. signs and symptoms to be detailed (seriousness, severity, frequency, time to onset, duration, risks and consequences))
- Key messages on how to prevent and minimise GI toxicity through appropriate monitoring (with reference to treatment journal) and management:
  - prophylactic treatment with antidiarrheal medicinal product
  - dietary changes
  - when to alert HCP and the importance of it for further treatment adjustment

- Remark on importance of reading the PIL
- Remarks on the importance of reporting ADRs

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE**

**1. NAME OF THE MEDICINAL PRODUCT**

Nerlynx 40 mg film-coated tablets  
neratinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film coated tablet contains neratinib maleate equivalent to 40 mg neratinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

180 tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not swallow the desiccant.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Keep the bottle tightly closed in order to protect from moisture.



**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Puma Biotechnology, Ltd.  
Bristol  
BS1 2NT  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER**

EU/1/18/1311/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Nerlynx 40 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Nerlynx 40 mg film-coated tablets neratinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of Section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

#### **What is in this leaflet**

1. What Nerlynx is and what it is used for
2. What you need to know before you take Nerlynx
3. How to take Nerlynx
4. Possible side effects
5. How to store Nerlynx
6. Contents of the pack and other information

#### **1. What Nerlynx is and what it is used for**

##### **What Nerlynx is**

Nerlynx contains the active substance ‘neratinib’. It belongs to a group of medicines called ‘tyrosine kinase inhibitors’ used to block cancer cells and treat breast cancer.

##### **What Nerlynx is used for**

Nerlynx is used for patients who have early stage breast cancer which:

- is human epidermal growth factor receptor 2-positive (HER2-positive) and
- has previously been treated with another medicine called ‘trastuzumab’.

The ‘HER2 receptor’ is a protein found on the surface of cells in the body. It helps control how a healthy breast cell grows. In HER2-positive breast cancer, the cancer cells have a large amount of HER2 receptors on their surface. This results in the cancer cells dividing and growing faster.

Before Nerlynx is used, your cancer must have been tested to show it is HER2-positive. You must also have previously been treated with trastuzumab.

##### **How Nerlynx works**

Nerlynx works by blocking the HER2 receptors on the cancer cells. This helps to stop the cells from dividing and growing.

## **2. What you need to know before you take Nerlynx**

### **Do not take Nerlynx**

- if you are allergic to neratinib or any of the other ingredients of this medicine (listed in Section 6).

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Nerlynx.

### **You need to take an anti-diarrhoea medicine when you start Nerlynx**

Nerlynx can cause diarrhoea early during treatment. You should take an anti-diarrhoea medicine so that your diarrhoea does not become severe, and to prevent you from getting dehydrated during treatment with Nerlynx.

### **Tests and checks for liver problems**

Nerlynx can cause changes in liver function – these are shown in blood tests. Your doctor will do blood tests before and during your treatment with Nerlynx. Your doctor will stop your treatment with Nerlynx if your liver tests show severe problems.

### **Children and adolescents**

Do not use in children under 18 years of age. The safety of Nerlynx and how effective it is has not been studied in this age group.

### **Other medicines and Nerlynx**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Nerlynx can affect the way some other medicines work. Also some other medicines can affect the way Nerlynx works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:

- ketoconazole - a medicine for fungal infections
- rifampin - a medicine for tuberculosis (TB)
- digoxin - a medicine for heart problems
- medicines for stomach problems such as:
  - lansoprazole, omeprazole or similar medicines called ‘proton pump inhibitors’ or PPIs and ranitidine, cimetidine or similar medicines called ‘H2 receptor antagonists’ are not recommended.
  - antacid medicines - the dose of these medicines and Nerlynx should be separated by at least 3 hours.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Nerlynx.

### **Nerlynx with food and drink**

Do not take grapefruit while you are taking Nerlynx – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because the grapefruit may interact with Nerlynx and affect how the medicine works.

### **Pregnancy**

If you are pregnant, the doctor will assess the potential benefit to you and risk to the foetus before giving this medicine to you. If you become pregnant while taking this medicine, the doctor will assess the potential benefit to you and the risk to the foetus, of continuing this medicine.

### **Contraception**

Women who can become pregnant must use an effective method of contraception, including a barrier method:

- while taking Nerlynx and
- for one month after treatment has finished.

Men must use an effective barrier method of contraception such as a condom:

- while taking Nerlynx and
- for three months after treatment has finished.

### **Breast-feeding**

Talk to your doctor before taking Nerlynx if you are breast-feeding or plan to breast-feed because small amounts of this medicine may pass into your breast milk. Your doctor will discuss with you the benefits and risks of taking Nerlynx during this time.

### **Driving and using machines**

Nerlynx has minor or moderate influence on the ability to drive and use machines. The side effects of Nerlynx (for example, dehydration and dizziness resulting from diarrhoea, fatigue, and fainting) may affect how tasks that require judgment, motor or cognitive skills are carried out.

## **3. How to take Nerlynx**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

### **How much Nerlynx to take**

The recommended dose of Nerlynx is 6 tablets once a day (a total of 240 mg).

- Take the tablets with food. Do not crush or dissolve. Do not swallow the desiccant.
- Take all the tablets with water, at about the same time each day, preferably in the morning.

The course of treatment is one year.

### **You need to take an anti-diarrhoea medicine when you start Nerlynx**

Nerlynx can cause diarrhoea early during treatment unless anti-diarrhoea medicine is taken to prevent or reduce diarrhoea. Diarrhoea usually happens early in treatment with Nerlynx and may be severe, causing you to get dehydrated.

- Start taking anti-diarrhoea medicine with the first dose of Nerlynx.
- Your doctor will tell you how to take the anti-diarrhoea medicine.
- Keep taking anti-diarrhoea medicine during the first one to two months of Nerlynx treatment. Your doctor will tell you if you need to keep taking anti-diarrhoea medicine after the first two months to control your diarrhoea.
- Your doctor will also tell you if you need to change the dose of Nerlynx because of diarrhoea.

**If you take more Nerlynx than you should**, contact a doctor or a hospital straight away. Take the medicine pack with you.

Some side effects associated with taking more Nerlynx than you should are: diarrhoea, nausea, vomiting and dehydration.

### **If you forget to take Nerlynx**

- If you forget a dose, wait until the next day before you take the next dose.
- Do not take a double dose to make up for a forgotten dose.

### **If you stop taking Nerlynx**

- Do not stop taking Nerlynx without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

##### **Diarrhoea**

Nerlynx can cause diarrhoea early during treatment unless anti-diarrhoeal medicines are taken to prevent or reduce diarrhoea. The diarrhoea may be severe, and you may get dehydrated. See Section 3 for more information about the anti-diarrhoea medicine you need to take at the same time as Nerlynx.

##### **Talk to your doctor if:**

- you are having diarrhoea that does not go away - they can advise how to control your diarrhoea.
- you feel dizzy or weak from diarrhoea - alternatively go to the hospital immediately.

##### **Liver problems**

Nerlynx can cause changes in liver function - these are shown in blood tests. You may or may not have signs or symptoms of liver problems (e.g., yellow skin and/or eyes, dark urine, or light-colour stools). Your doctor will do blood tests before and during your treatment with Nerlynx. Your doctor will stop your treatment with Nerlynx if your liver tests show severe problems.

##### **Other side effects**

Tell your doctor or pharmacist if you notice any of the following side effects:

**Very common:** may affect more than 1 in 10 people

- diarrhoea
- stomach pain, feeling or being sick, low appetite
- dry or inflamed mouth, including blisters or mouth ulcers
- rash
- muscle spasms or cramps
- feeling very tired

**Common:** may affect up to 1 in 10 people

- burning sensation during urination and frequent, and urgent need to urinate, (may be symptoms of urinary tract infection)
- dehydration
- nosebleed
- mild stomach upset
- dry mouth
- changes in liver blood test results
- nail problems including nail splitting or colour change
- dry skin including cracked skin
- changes in kidney function test
- weight loss

**Uncommon:** may affect 1 in 1000 people

- kidney failure
- changes in liver blood test results (i.e., blood bilirubin increased)

Tell your doctor or pharmacist if you notice any of the side effects above.

##### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system**

listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Nerlynx**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

Do not use Nerlynx if you notice any signs of damage to the packaging or if there are any signs of tampering (e.g., inner seal is broken).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Nerlynx contains**

- The active substance is neratinib. Each film-coated tablet contains neratinib maleate, equivalent to 40 mg neratinib.
- The other ingredients are:
  - Tablet core: mannitol (E421), microcrystalline cellulose, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate
  - Tablet coating: polyvinyl alcohol, titanium dioxide (E171), macgrol, talc, iron oxide red (E172)

### **What Nerlynx looks like and contents of the pack**

The film-coated tablets are red oval shaped and debossed with 'W104' on one side and plain on the other side.

Nerlynx film-coated tablets are packaged in a white, high-density polyethylene (HDPE) round bottle with child-resistant, polypropylene closure, and foil induction inner seal for a tamper-evident seal. Each bottle contains 180 film-coated tablets.

An HDPE desiccant canister with 1 g silica gel is enclosed with the tablets in each bottle. Do not swallow the desiccant.

### **Marketing Authorisation Holder**

Puma Biotechnology, Ltd.  
11th Floor, Whitefriars, Lewins Mead  
Bristol  
BS1 2NT  
United Kingdom

**Manufacturer**

AndersonBrecon  
(UK) Limited  
Pharos House, Wye Valley Business Park  
Brecon Road, Hay-on-Wye  
Hereford HR3 5PG  
United Kingdom

**This leaflet was last revised in MM/YYYY**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

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