1.3.1.1 Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NERLYNX 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar alcohol: Each tablet contains 36 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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 indications

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

4.2 Posology and method of administration

NERLYNX treatment should be initiated and supervised by a medical practioner experienced in the administration of anti-cancer medicines.

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 1, Table 2, Table 3, and Table 4.

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†	**Action**
Grade 3	Stop NERLYNX until recovery to Grade 0 – 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

† Per CTCAE v4.0

Dose modifications for diarrhoea:

Diarrhoea management requires the correct use of an anti-diarrhoeal medicine 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**
• Grade 1 diarrhoea [increase of < 4 stools per day over baseline] • Grade 2 diarrhoea [increase of	• Adjust anti-diarrhoeal treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration

4 – 6 stools per day over baseline] lasting < 5 days • Grade 3 diarrhoea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalisation indicated; limiting self-care activities of daily living] lasting ≤ 2 days	• Once event resolves to Grade 0 – 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent NERLYNX administration (refer to section 4.4).
• Any grade with complicated features† • Grade 2 diarrhoea lasting 5 days or longer‡ • Grade 3 diarrhoea lasting between 2 days and 3 weeks‡	• Interrupt NERLYNX treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • If diarrhoea resolves to Grade 0 – 1 in one week or less, then resume NERLYNX treatment at the same dose. • If diarrhoea resolves to Grade 0 – 1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 1). • Once event resolves to Grade 0 – 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent NERLYNX administration (refer to section 4.4). • If grade 3 diarrhoea persists longer than 3 weeks, discontinue NERLYNX permanently.

• Grade 4 diarrhoea [life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
• Diarrhoea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment

* 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 4 (see section 4.4).

Table 4: Dose modifications for hepatotoxicity

Severity of hepatotoxicity*	**Action**
• Grade 3 ALT (> 5 – 20 x ULN) OR • Grade 3 bilirubin (>3 - 10 x ULN)	• Stop NERLYNX until recovery to Grade 0 – 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to Grade 0 – 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX.
• Grade 4 ALT (> 20 x ULN) OR	• Permanently discontinue NERLYNX • Evaluate alternative causes

• Grade 4 bilirubin (> 10 x ULN)	

ULN = upper limit normal

ALT = alanine aminotransferase

* Per CTCAE v4.0

Missed doses:

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

Grapefruit and pomegranate:

Concomitant administration of neratinib with grapefruit or pomegranate/grapefruit or pomegranate juice is not recommended (see sections 4.4 and 4.5).

Use of CYP3A4/P-gp inhibitors:

If the inhibitor cannot be avoided, reduce NERLYNX dose:

- to 40 mg (one 40 mg tablet) taken once daily with a strong CYP3A4/P-gp inhibitor,
- to 40 mg (one tablet) taken once daily with a moderate CYP3A4/P-gp.

If well tolerated, increase to 80 mg for at least 1 week, then to 120 mg for at least 1 weeks, and to 160 mg as a maximal daily dose. Patient should be monitored carefully, especially GI effect including diarrhoea and hepatotoxicity.

After discontinuation of a strong or moderate CYP3A4/P-gp inhibitor, resume previous dose of NERLYNX 240 mg (see sections 4.4, 4.5 and 5.2).

H_2 receptor antagonists and antacids:

If H_2 receptor antagonists are used, NERLYNX should be taken at least 2 hours before or 10 hours after the intake of the H_2 receptor antagonist. Separate dosing of NERLYNX and antacids by at least 3 hours should be applied (see sections 4.4, 4.5 and 5.2).

Special populations

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 (see section 5.2).

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 neratinib maleate or to any of the excipients of NERLYNX (see section 6.1).

Co-administration with the following medicines that are strong or moderate inducers of the CYP3A4/P-gp isoform of cytochrome P450, such as (see sections 4.5 and 5.2):

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

Severe hepatic impairment (Child-Pugh C) (see section 5.2).

4.4 Special warnings and precautions for use

Diarrhoea:

Diarrhoea has been reported during treatment with NERLYNX (see sections 4.2 and 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 medicine with the first dose of NERLYNX, and maintain regular dosing of the anti-diarrhoeal medicine during the first 1 – 2 months of NERLYNX treatment, titrating to 1 – 2 bowel movements per day.

Elderly:

Elderly patients (≥ 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 sections 4.2 and 5.2).

Liver function:

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 ≥ 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_2 receptor antagonists and antacids:

Treatments that increase gastrointestinal pH may lower the absorption of neratinib, thus decreasing systemic exposure. Co-administration with proton pump inhibitors (PPIs) is not recommended (see sections 4.5 and 5.2).

In case of H_2 receptor antagonists or antacids, modalities of administration should be adapted (see sections 4.2, 4.5 and 5.2).

Pregnancy:

Neratinib may cause fetal 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 or moderate CYP3A4 and P-gp inhibitors is not recommended due to risk of increased exposure to neratinib. If the inhibitor cannot be avoided, NERLYNX dose adjustment should be applied (see sections 4.2, 4.5 and 5.2).

Grapefruit or pomegranate juice should be avoided during treatment with NERLYNX (see sections 4.2 and 4.5).

Concomitant treatment with moderate inducers of CYP3A4 and P-gp:

Concomitant treatment with moderate CYP3A4 and P-gp inducer is not recommended as it may lead to a loss of neratinib efficacy (see sections 4.5 and 5.2).

Concomitant treatment with substrates of P-gp:

Patients who are treated concomitantly with therapeutic medicines with a narrow therapeutic window whose absorption involves P-gp transporters in the gastrointestinal tract should be carefully monitored (see sections 4.5 and 5.2).

4.5 Interactions with other medicines and other forms of interaction

Effects of other substances on neratinib

Neratinib is primarily metabolised by CYP3A4 and is a P-gp substrate.

CYP3A4/P-gp inducers:

Clinical study demonstrated that concomitant use of strong CYP3A4/P-gp inducers significantly decreased neratinib exposure, therefore concurrent use of neratinib with strong CYP3A4/P-gp inducers is contraindicated (e.g. strong inducers: phenytoin, carbamazepine, rifampicin, or herbal preparations containing St John's wort *(Hypericum perforatum)*). Concurrent use of neratinib with moderate CYP3A4/P-gp inducers is not recommended as it may also lead to loss of efficacy (e.g. moderate inducers: bosentan, efavirenz, etravirine, phenobarbital (phenobarbitone), primidone, dexamethasone) (see sections 4.3 and 5.2).

CYP3A4/P-gp inhibitors:

Clinical study and model-based predictions have demonstrated that concomitant use of strong or moderate CYP3A4/P-gp inhibitors significantly increased neratinib systemic exposure, therefore, concomitant use of neratinib with strong and moderate CYP3A4/P-gp inhibitors is not recommended (e.g. strong inhibitors: atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, lopinavir, ketoconazole, itraconazole, clarithromycin, troleandomycin, voriconazole and cobicistat; moderate inhibitors: ciprofloxacin, cyclosporine, diltiazem, fluconazole, erythromycin, fluvoxamine and verapamil). If the inhibitor cannot be avoided, NERLYNX dose adjustment should be applied (see sections 4.2, 4.4 and 5.2).

Grapefruit/pomegranate or grapefruit/pomegranate juice may also increase neratinib plasma concentrations and should be avoided (see sections 4.2 and 4.4).

Proton pump inhibitors, H_2 receptor antagonists and antacids

The *in vitro* solubility of neratinib is pH-dependent. Concomitant treatment with substances that increase gastric pH may lower the absorption of neratinib, thus decreasing systemic exposure. Co-

administration with proton pump inhibitors (PPIs) is not recommended (e.g. omeprazole or lansoprazole) (see sections 4.4 and 5.2).

NERLYNX should be taken at least 2 hours before or 10 hours after the intake of the H_2 receptor antagonist (see sections 4.2, 4.4 and 5.2).

Separate dosing of NERLYNX with antacids by at least 3 hours (see sections 4.2, 4.4 and 5.2).

Anti-diarrhoeal loperamide

Clinical study has demonstrated that there were no clinically significant differences in the exposure of subjects to neratinib with or without concurrent dosing with loperamide (see section 5.2).

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).

P-glycoprotein efflux transporter:

In vitro studies demonstrated that neratinib is an inhibitor of P-glycoprotein (P-gp) efflux transporters. This has been confirmed by clinical study using digoxin as probe substrate leading to an increase of 54 and 32 % in C_{max} and AUC, respectively. This might be clinically relevant for patients who are treated concomitantly with therapeutic medicines with a narrow therapeutic window whose absorption involves P-gp transporters in the gastrointestinal tract (e.g. digoxin, colchicine, dabigatran, phenytoin, statins, ciclosporin, everolimus, sirolimus, tacrolimus). They should be carefully monitored (see sections 4.4 and 5.2).

Breast cancer resistance protein efflux transporter:

Neratinib may inhibit breast cancer resistance protein (BCRP) at intestinal level as suggested by *in vitro* studies. A clinical study with BCRP substrates has not been conducted. As co-administration of neratinib with BCRP substrates may lead to an increase of their exposure, patients who are treated with BCRP substrates (e.g. rosuvastatin, sulfasalazine and irinotecan) should be monitored carefully (section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Based on findings in animals, neratinib may cause fetal 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-fetal lethality and fetal 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 fetus.

Breastfeeding

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 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 (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1 000 to <1/100)

Rare (≥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
Infections and infestations	Common	Urinary tract infection
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration
Nervous system disorders	Common	Syncope
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis

Gastrointestinal disorders	Very Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal pain upper, and stomatitis[1]
	Common	Abdominal distension, dry mouth and dyspepsia
Hepatobiliary disorders	Common	Alanine aminotransferase increased, and aspartate aminotransferase increased
	Uncommon	Blood bilirubin increased
Skin and subcutaneous tissue disorders	Very Common	Rash[2]
	Common	Nail disorder[3], skin fissures and dry skin
Musculoskeletal and connective tissue disorders	Very Common	Muscle spasms
Renal and urinary disorders	Common	Blood creatinine increased
	Uncommon	Renal failure
General disorders and administration site conditions	Very Common	Fatigue
Investigations	Common	Weight decreased

[1] Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering and mucosal inflammation.

[2] Includes rash, rash erythematous, rash follicular, rash generalised, rash pruritic and rash pustular.

[3] Includes nail disorder, paronychia, onychoclasis, 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 were 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, 1 236 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 1 710 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 erythrodysaesthesia syndrome (9,9 % vs 1,0 %), and dermatitis acneiform (6.0 % vs 1,0 %).

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: http:/www.sahpra.org.za/Publications/Index/8

To report any adverse reactions to Pierre Fabre (Pty) Ltd, please contact 087 654 2049 or RAZA@pierre-fabre.com or your pharmacist.

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

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors.

ATC code: L01XE45/A 26 Cytostatics.

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 signalling pathways, and potently inhibits tumour cell proliferation *in vitro*. Neratinib

inhibited EGFR and/or HER2-expressing carcinoma cell lines with a cellular IC50 <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 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, 57,7 % had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 27,2 % were node negative, 41,5 % had one to three positive nodes and 29,4 % 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-randomisation demonstrated that NERLYNX significantly reduced the risk of invasive disease recurrence or death by 33 % (HR=0,67 with 95 % CI (0,49, 0,91), two-sided p = 0,011) in the ITT population.

Table 6: Primary 2-year efficacy results – ITT and hormone receptor positive populations who were less than one year from completion of trastuzumab therapy

Variable	**Estimated 2-year event free rates[1] (%)**		**Hazard ratio (95 % CI)[2]**	**P-value[3]**
ITT population				
	NERLYNX (N = 1 420)	**Placebo (N = 1 420)**		
Invasive disease-free survival	94,2	91,9	0,67 (0,49, 0,91)	0,011
Disease-free survival including ductal carcinoma *in situ*	94,2	91,3	0,62 (0,46, 0,84)	0,002
Distant disease-free survival	95,3	94,0	0,75 (0,53, 1,06)	0,110
Time to distant recurrence	95,2	94,2	0,74 (0,52, 1,06)	0,102
CNS recurrence	0,92	1,16	–	0,586
	Hormone receptor positive population who were less than one year from completion of trastuzumab			
	NERLYNX (N = 671)	**Placebo (N = 668)**	**Hazard ratio (95 % CI)[4]**	**P-value[5]**
Invasive disease-free survival	95,3	90,9	0,50 (0,31, 0,78)	0,003

Disease-free survival including ductal carcinoma *in situ*	95,3	90,1	0,45 (0,28, 0,71)	< 0,001
Distant disease-free survival	96,1	93,0	0,53 (0,31, 0,88)	0,015
Time to distant recurrence	96,3	93,3	0,53 (0,30, 0,89)	0,018
CNS recurrence	0,34	1,01	-	0,189

CNS = central nervous system.

[1] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.

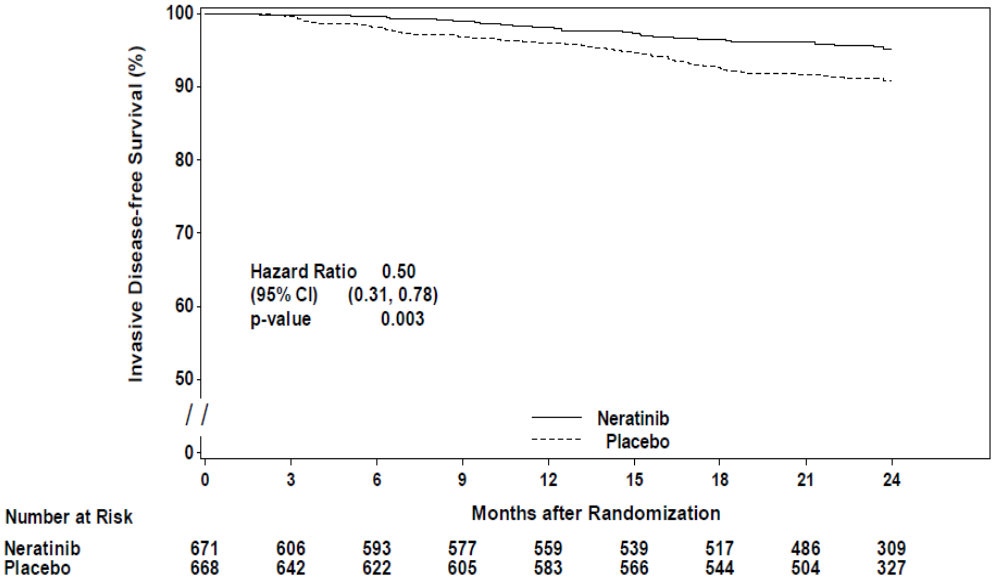
[2] Stratified Cox proportional hazards model

[3] Stratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

[4] Unstratified Cox proportional hazards model

[5] 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 invasive disease-free survival – hormone receptor positive population who were less than one year from completion of trastuzumab therapy

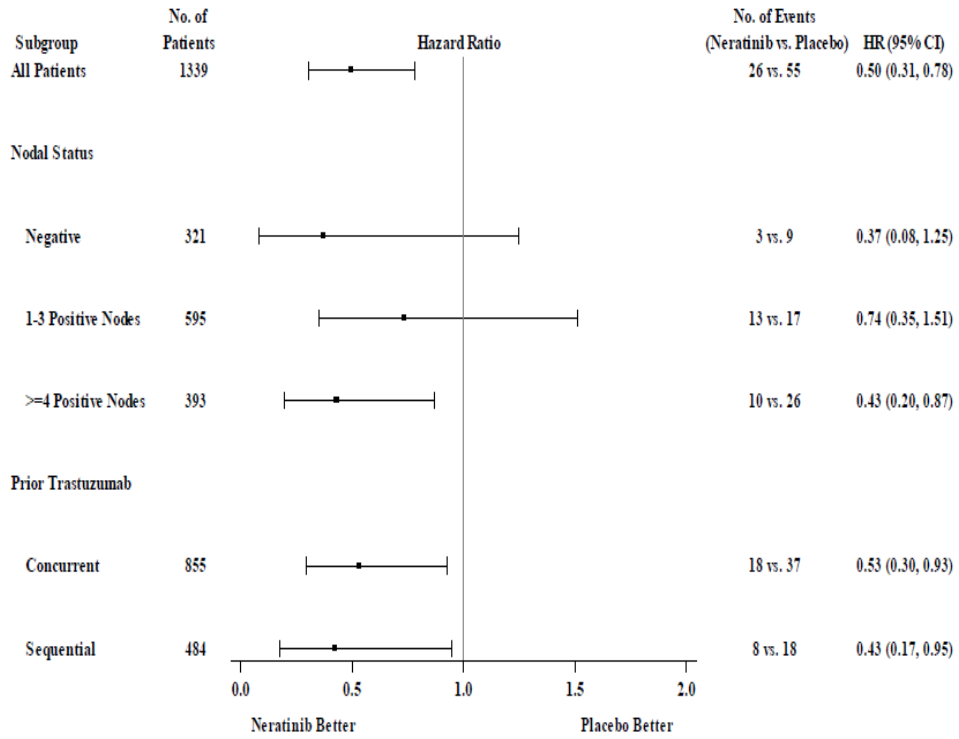


Approximately 75 % of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. While the treatment benefit of NERLYNX over placebo was maintained at five years, the effect size cannot be reliably estimated.

In patients that were hormone receptor negative, regardless of time from trastuzumab therapy, the hazard ratio for iDFS at 2 years was 0,94, with 95 % CI (0,61, 1,46). In this population, efficacy has not been demonstrated.

For hormone receptor positive patients, the invasive disease-free survival of NERLYNX within pre-specified patient subgroups is presented in Figure 2.

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



Note: Patients (n = 30) who had an unknown nodal status are not shown because the HR could not be estimated

Paediatric population

No data available.

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 %. In a mass balance study, the total recovery (urinary and fecal excretion) of intact neratinib and metabolites demonstrates that the fraction absorbed for neratinib is at least 10 % and likely more than 20 %. Moreover, model-based predictions suggested an overall absorbed fraction from the gut (fa) of 26 %.

In vitro neratinib solubility is pH-dependent. Treatments that increase gastrointestinal pH may lower the absorption of neratinib, thus decreasing systemic exposure.

Distribution

Binding of neratinib to human plasma proteins, including covalent binding to human serum albumin (HSA), was greater than 98 % and independently of the tested neratinib concentration. Neratinib bound predominantly to HSA and human alpha-1 acid glycoprotein (AAG). Binding of M6 main metabolite (M6) to human plasma proteins was greater than 99 % and independently of the tested M6 concentrations.

In vitro studies demonstrated that neratinib is a substrate for P-glycoprotein (P-gp) (see sections 4.2, 4.3, 4.4 and 4.5) and BCRP. *In vitro* studies demonstrated that neratinib and its main metabolite M6 are not substrates of hepatic uptake transporters OATP1B1*1a and OATP1B3 at 10 µM.

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 amongst circulating metabolites (M2, M3, M6, M7 and M11) none is above

8 % of neratinib plus metabolite total exposure after oral administration of neratinib. 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. Based on steady state exposures, neratinib provides the majority of pharmacological activity (73 %), with 20 % provided by exposure to M6, 6 % provided by M3, and negligible contribution (< 1 %) from M7 and M11 AUC.

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 240 mg neratinib oral solution, 95,5 % and 0,96 % of the administered dose was recovered in the faeces and urine, respectively.

The excretion was rapid and complete, with most of the dose recovered in faeces within 48 hours and 96,5 % of total radioactivity recovered in excreta after 8 days.

Unchanged neratinib was the most abundant species in excreta accounting for 62,1 % of total dose recovered in excreta. The most abundant metabolites in faeces were M6 (19,7 % of administered dose), followed by M2, M3 and M7, all below 10 % of administered dose.

Medicine interactions

Effect of CYP3A4/P-gp inducer on neratinib:

Following concomitant administration of 240 mg neratinib with repeated doses of 600 mg rifampicin, a strong CYP3A4/P-gp inducer, neratinib exposures were significantly decreased by 76 % and 87 % for C_{max} and AUC, respectively, compared with neratinib administration alone (see sections 4.3 and 4.5).

Effect of CYP3A4/P-gp inhibitor on neratinib:

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/P-gp inhibitor, increased neratinib systemic exposure by 3,2- and 4,8-fold for C_{max} and AUC, respectively, compared with neratinib administered alone.

Model-based predictions suggested that co-administration of a single oral dose of 240 mg of neratinib in the presence of fluconazole (200 mg once daily for 8 days), a moderate CYP3A4/P-gp inhibitor, increased neratinib systemic exposure by 1,3- and 1,7-fold for C_{max} and AUC, compared with neratinib administered alone.

Model-based predictions suggested that co-administration of a single oral dose of 240 mg of neratinib in the presence of verapamil (120 mg twice daily for 8 days), a moderate CYP3A4/strong P-gp inhibitor, increased neratinib systemic exposure by 3,0- and 4,0-fold for C_{max} and AUC, compared with neratinib administered alone (see sections 4.2, 4.4 and 4.5).

Effect of gastric pH modifiers on neratinib:

Co-administration of lansoprazole or ranitidine (1 x 300 mg) with a 240 mg single dose of neratinib in healthy volunteers resulted in a decreased neratinib exposure by around 70 % or 50 %, respectively. The magnitude of ranitidine interaction on neratinib AUC was reduced by around 25 %, by staggering the administration of ranitidine (2 x 150 mg) 2 hours after neratinib administration (see sections 4.2, 4.4 and 4.5).

Effect of other treatment on neratinib:

There were no apparent clinically relevant medicine interactions observed for neratinib when administered concomitantly with capecitabine, paclitaxel, trastuzumab, vinorelbine, or antidiarrheals (loperamide) (see section 4.5).

Effect of neratinib on CYP substrates:

Neratinib and metabolite M6 were not potent direct inhibitors of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4. Time-dependent inhibition of CYP3A4 and CYP2B6 by neratinib and M6 could not be excluded. Neratinib did not induce CYP1A2, 2B6, 2C9, or 3A4.

Effect of neratinib on transporters:

There was no clinically relevant inhibition of human BSEP efflux transporter activity *in vitro*, with a reported IC50 value of >10 µM. Neratinib at 10 µM appeared to inhibit the BCRP efflux transporter which could be clinically relevant at intestinal level (see section 4.5).

In *in vitro* studies, neratinib was an inhibitor of P-glycoprotein (P-gp) efflux transporters, which was further confirmed in a clinical study. Multiple oral doses of neratinib 240 mg increase digoxin exposures (54 and 32 % increase in C_{max} and AUC, respectively) with no impact on its renal clearance level (see sections 4.4 and 4.5).

Neratinib produced no inhibitory activity towards the uptake transporters, OATP1B1*1a, OATP1B3, OAT1, OAT3 and OCT2, with reported IC50 values were > 10µM. Neratinib produced inhibitory activity in OCT1 uptake transporter, with an IC50 of 2.9 µM.

Special populations

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 (see sections 4.2 and 4.4)

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 (see sections 4.2 and 4.3).

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-foetal 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

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

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

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 and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 – Eleventh Avenue

Houghton Estate

2198

RSA

8. REGISTRATION NUMBER

55/26/0541

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 January 2023.

10. DATE OF REVISION OF THE TEXT

09 October 2024