ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

Nerlynx should be discontinued 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 ≤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 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**
• Grade 1 diarrhoea [increase of < 4 stools per day over baseline] • Grade 2 diarrhoea [increase of 4-6 stools per day over baseline] lasting < 5 days • Grade 3 diarrhoea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤ 2 days	• Adjust anti-diarrhoeal treatment • Diet modifications • Fluid intake of ~2 L/day should be maintained to avoid dehydration • 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).

Severity of diarrhoea*	Action
• 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/day should be maintained to avoid dehydration • If diarrhoea resolves to Grade ≤1 in one week or less, then resume Nerlynx treatment at the same dose. • If diarrhoea resolves to Grade ≤1 in longer than one week, then resume Nerlynx treatment at reduced dose (see Table 1). • 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). • If grade 3 diarrhoea persists longer than 3weeks, 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 ≤1 • Evaluate alternative causes • Resume Nerlynx at the next lower dose level if recovery to Grade ≤1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue Nerlynx. • If grade 3 hepatotoxicity persists longer than 3 weeks, discontinue Nerlynx permanently
• Grade 4 ALT (>20 x ULN) OR • Grade 4 bilirubin (>10 x ULN)	• Permanently discontinue Nerlynx • Evaluate alternative causes

ULN=Upper Limit Normal; ALT= Alanine Aminotransferase
* Per CTCAE v4.0

Missed dose
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 inhibitor. If well tolerated, increase to 80 mg for at least 1 week, then to 120 mg for at least 1 week, and to 160 mg as a maximal daily dose. Patient should be monitored carefully, especially GI effects 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 of 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. The tablets 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/P-gp isoform of cytochrome P450, such as (see sections 4.5 and 5.2):
- carbamazepine, 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 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 (≥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 intraveinous 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 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 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 and pomegranate
Grapefruit or pomegranate juice may inhibit CYP3A4 and/or P-gp and 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 inducers 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 agents 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 Interaction with other medicinal products and other forms of interaction

Effects of other substances on neratinib

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

CYP3A4/P-gp inducers
A 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, primidone, dexamethasone) (see sections 4.3 and 5.2).

CYP3A4/P-gp inhibitors
A 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, cyclosporin, diltiazem, fluconazole, erythromycin, fluvoxamine and verapamil). If the inhibitor can not be avoided, Nerlynx dose adjustment shoud 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 section 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 and antacids by at least 3 hours (see sections 4.2, 4.4 and 5.2).

Antidiarrhoeal loperamide
A 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 transporters
In-vitro studies demonstrated that neratinib is an inhibitor of P-glycoprotein (P-gp) efflux transporters. This has been confirmed by a clinical study using digoxin as probe substrate leading to an increase of 54 and 32% in Cmax and AUC, respectively. This might be clinically relevant for patients who are treated concomitantly with therapeutic agents with a narrow therapeutic window whose absorption involves P-gp transporters in the gastrointestinal tract (e.g. digoxin, colchicine, dabigatran, phenytoin, statins, cyclosporine, 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 (see section 5.2).

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 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 (≥ 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

System Organ Class	Frequency	Adverse Drug Reaction
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 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, 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 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, protein kinase inhibitors, ATC code: L01EH02

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 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).

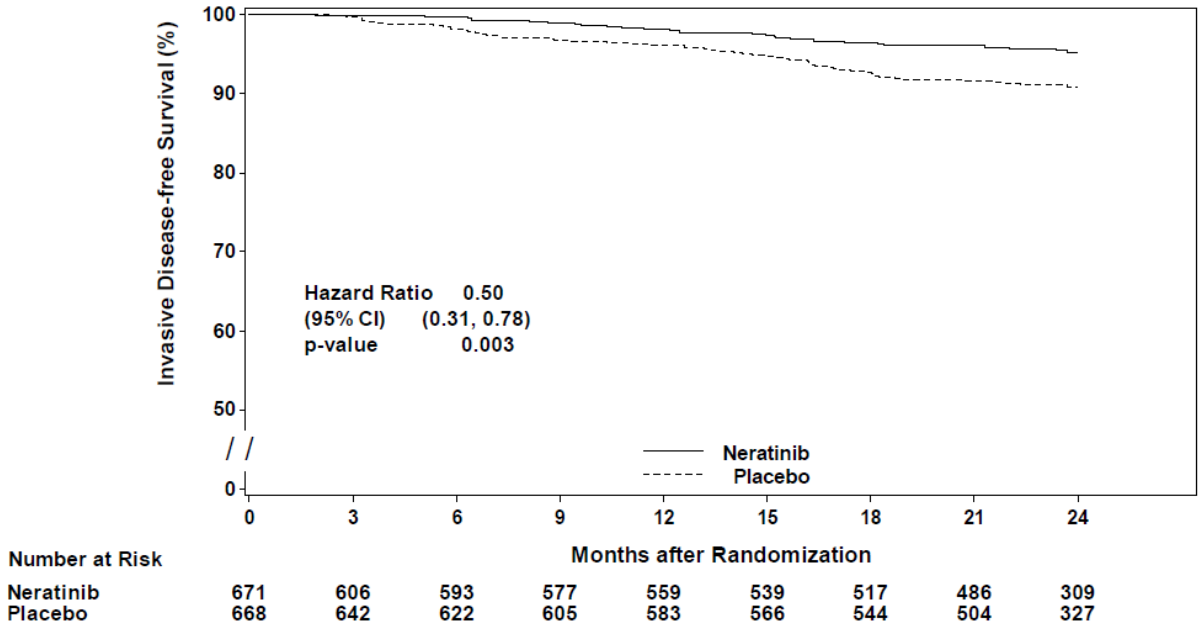
The primary analysis of the study after 2 years post-randomisation demonstrated that Nerlynx significantly reduced the risk of invasive disease recurrence or death by 33% (HR=0.67 with 95% CI (0.49, 0.91), two-sided p = 0.011) in the ITT population.

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=1420)	**Placebo (N=1420)**		
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	95.5	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

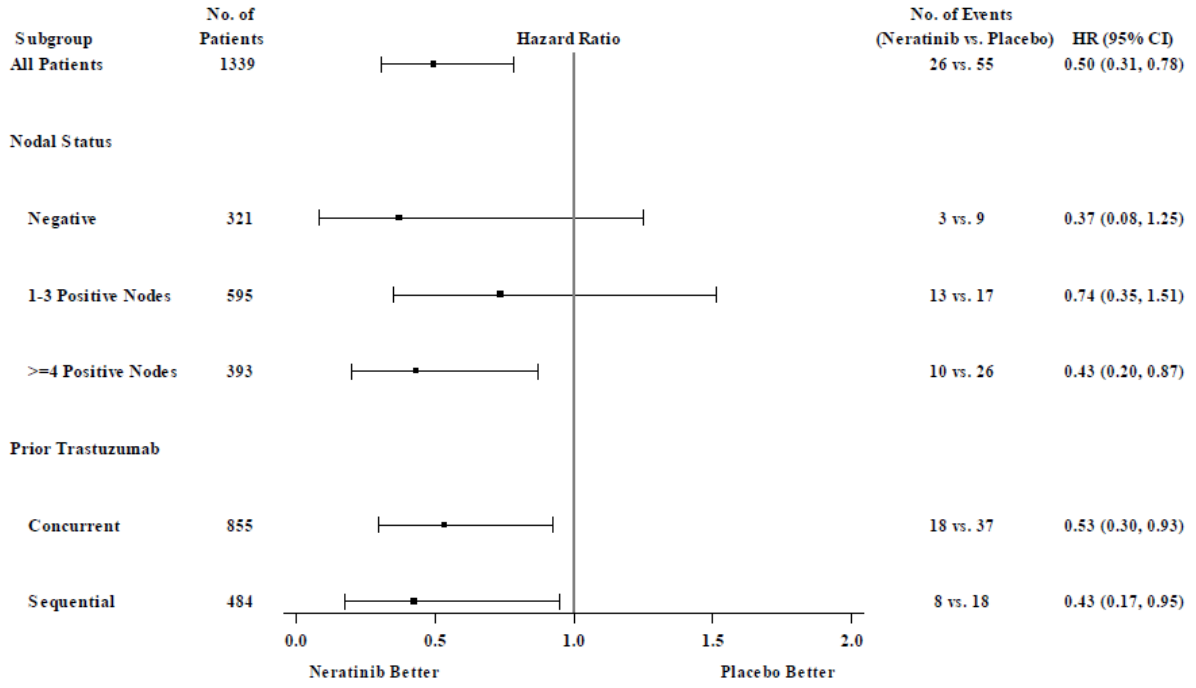
CNS = central nervous system.
[1] Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.
[2] Stratified Cox proportional hazards model
[3] Stratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.
[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



For hormone receptor positive patients who were less than one year from completion of trastuzumab therapy, the relative treatment benefit of Nerlynx within pre-specified patient subgroups is presented in Figure 2.

Figure 2: Hormone receptor positive patients who were less than one year from completion of trastuzumab therapy, 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

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.

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.

The median OS follow-up time for the ITT population was 8.06 years, 8.03 years in the neratinib arm and 8.10 years in the placebo arm, with a total of 1542 (54.3%) patients followed up for survival for 8 or more years, 746 (52.5%) in the neratinib arm and 796 (56.1%) in the placebo arm. The number of deaths was 264 (9.3%), with 127 (8.9%) in the patients treated with neratinib and 137 (9.6%) in the patients treated with placebo.
There was no statistically significant difference in overall survival between the Nerlynx and the placebo arm [HR 0.96 (95% CI: 0.75, 1.22)] in the ITT population at a median follow-up of 8.06 years.

In the hormone receptor positive population who were less than one year from completion of trastuzumab therapy, the median follow-up was 8.0 years in the neratinib arm and 8.1 years in the placebo arm, with a total of 1 339 (47.1%) patients followed up for survival for 8 or more years, 671 (23.6%) in the neratinib arm and 668 (23.5%) in the placebo arm. In this subpopulation the number of deaths was 55 (8.2%) in the patients treated with neratinib and 68 (10.2%) in the patients treated with placebo [HR 0.83 (95% CI, 0.58, 1.18)].

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 13%, 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 independent 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 independent 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 relevant clinical concentration.

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 primarily 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.

Medicinal product 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 Cmax 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 Cmax 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 inhibitor, increased neratinib systemic exposure by 1.3- and 1.7-fold for Cmax 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 Cmax 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 (1x300 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 (2x150 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 drug-drug interactions observed for neratinib when administered concomitantly with capecitabine, paclitaxel, trastuzumab, vinorelbine, or antidiarrhoeals (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 and no time-dependent inhibition is expected.
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 increased 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.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that neratinib has an evident potential to be persistent, bioaccumulative, and toxic to the environment (see section 6.6).

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

3 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

60 mL white 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

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1311/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2018
Date of latest renewal: 26 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

Pierre Fabre Médicament Production – Cahors
Site de Cahors
Le Payrat
46000 Cahors
FRANCE

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.

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 (diarrhoea)" (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 antidiarrhoeal 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 (diarrhoea) (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 antidiarrhoeal 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

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

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

Carton
nerlynx 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Carton
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Carton
PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Nerlynx 40 mg film-coated tablets
neratinib

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

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 hormone receptor positive (HR-positive) and human epidermal growth factor receptor 2-positive (HER2) overexpressed/amplified (HER2 positive), and
- has previously been treated with trastuzumab based therapy that ended less than one year ago.

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- overexpressed/amplified breast cancer, the cancer cells have an increased amount of HER2 receptors on their surface. This results in the cancer cells dividing and growing faster.
'Hormone receptors' are also proteins expressed inside the cells of some specific tissues. Estrogens and progesterone bind to these proteins and regulate cell activity. In HR-positive breast cancer, tumor cell division and growth can be enhanced by estrogens and/or progesterone.

Before Nerlynx is used, your cancer must have been tested to show it is HR-positive and HER2-overexpressed/amplified. You must also have previously been treated with trastuzumab based therapy.

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),
- if you have a severe liver problem (corresponding to class C on the Child-Pugh score),
- if you are taking a medicine that strongly induces liver enzymes (CYP3A4) and/or drugs transporter (P-gp) such as:
    - rifampicin (a medicine for tuberculosis (TB)),
    - carbamazepine or phenytoin (medicines for seizures),
    - St. John's wort (herbal product for depression).

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. It can appear more than one time. You should take an anti-diarrhoea medicine that your doctor has recommended so that your diarrhoea does not become severe, and to prevent you from getting dehydrated during treatment with Nerlynx. Dietary changes (including adapted fluid intake) and appropriate dose modifications of Nerlynx might be needed for diarrhoea management.

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.

You should be closely monitored by your doctor if you suffer from:
- Reduced kidney function
- Chronic gastrointestinal disorder
- Cardiac disorders or if you have history of heart disease,
- Skin and subcutaneous tissue disorders.

Elderly:
If you are 65 or over you should be closely monitored by your doctor.

Children and adolescents
Do not use in children and adolescents 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. The efficacy and/or safety of Nerlynx and/or other medicines might be modified when taken concomitantly. This is because Nerlynx can affect the way some other medicines work. Also some other medicines can affect the way Nerlynx works.
In some cases, dose modifications or close monitoring can be done by your doctor.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- rifampicin - a medicine for tuberculosis
- carbamazepine, phenobarbital, phenytoin or primidone - medicines for seizures
- St John's wort - an herbal product for depression
- ketoconazole, voriconazole, itraconazole or fluconazole - medicines for fungal infections
- erythromycin,clarithromycin, troleandomycin or ciprofloxacine - medicines for bacterial infections
- protease inhibitors (such as ritonavir, lopinavir, saquinavir, nelfinavir, atazanavir, indinavir, efavirenz, etravirine) or medicine used in combinaison with antiretroviral therapy in HIV (cobicistat) - antiviral medicines
- nefazodone – a medicine to treat depression

- diltiazem or verapamil - medicines for high blood pressure and chest pain
- bosentan – a medicine for high blood pressure in pulmonary arteria.
- dabigatran or digoxin - a medicine for heart problems
- Statin medicine (such as rosuvastatin) – a medicine to treat high cholesterolemia
- doxamethasone – an anti inflammatory medicine (corticosteroids)
- colchicine – an anti inflammatory medicine used in gout
- irinotecan – a medicine used in colorectal cancers
- sulfasalazine – an anti-inflammatory intestinal medicine
- cyclosporine, everolimus, sirolimus and tacrolimus - immunosuppressant medicine
- fluvoxamine – a drug used to treat depressive states and obsessive-compulse disorders
- medicines for stomach problems:
    - proton pump inhibitors'or PPIs are not recommended (such as lansoprazole, omeprazole)
    - "H2 receptor antagonists" (such as ranitidine). Nerlynx should be taken at least 2 hours before or 10 hours after the intake of the H2-receptor antagonist.
    - 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 or pomegranate while you are taking Nerlynx – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because these fruits 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 the 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 treatment with 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 it is unknown if 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 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 them.
- Take all the tablets with water, at about the same time each day, preferably in the morning.

The course of treatment is one year.
If you get side effects, your doctor may adjust the dose or stop treatment temporarily or permanently.

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 and recurrent, causing you to get dehydrated. Your doctor will tell you how to adapt your diet and fluid intake.
- Start taking the anti-diarrhoea medicine prescribed by your doctor 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 (increase in number per day and/or change in stool consistency) 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 treatment 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 . If your doctor is not available 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 sick (nausea), being sick (vomiting), decreased appetite
- inflammation of the lining of the 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, frequent and urgent need to urinate, (may be symptoms of urinary tract infection)
- dehydration
- fainting
- nosebleed
- mild stomach upset (bloating, indigestion)
- dry mouth
- changes in liver blood test results (enzymes named alanine aminotransferase and aspartate aminotransferase increased)
- nail problems including nail splitting or colour change
- dry skin including cracked skin
- changes in kidney function test
- weight loss

Uncommon (may affect up to 1 in 100 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.

This medicinal product does not require any special temperature storage conditions.
Keep the bottle tightly closed in order to protect from moisture.

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), macrogol, 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. Keep it inside the bottle.

Marketing Authorisation Holder
PIERRE FABRE MEDICAMENT
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Manufacturer
Pierre Fabre Médicament Production – Cahors
Site de Cahors
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Other sources of information

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