nerlynx®
(neratinib)

PHYSICIAN TREATMENT GUIDE

A therapy management guide to help support your patients receiving NERLYNX (neratinib)

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[1]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may experience via the national reporting system (Appendix V – European Medicines Agency – Europa EU) and/or to the Pharmacovigilance department of Pierre Fabre laboratories (www.pierre-fabre.com/en/pharmacovigilance).

This material is based on EU Product Information and does not replace the SmPC and the RMP Educational Materials. Please refer to the material approved in your country.

Pierre Fabre

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References:

1. Nerlynx (neratinib 40 mg film-coated tablets) Summary of Product Characteristics. Last update 06/2020.
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1 ABOUT NERLYNX

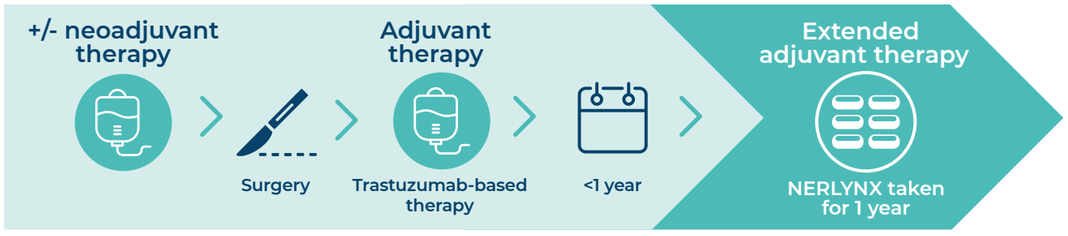
1.1 What is NERLYNX?

For nearly 20 years, patients with HER2+ breast cancer have benefited from the addition of trastuzumab-based therapy to chemotherapy[2,3] However, up to 31% face a disease-free survival event within 10 years after treatment.[3,4] Is there more that can be done to further reduce the risk of recurrence for HER2+/HR+ breast cancer after trastuzumab-based therapy?

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.[1]

Following adjuvant trastuzumab-based therapy, NERLYNX, as extended adjuvant therapy, offers an additional step up in the treatment of HER2+/HR+ breast cancer.[1,5,6]

Introducing NERLYNX as extended adjuvant therapy

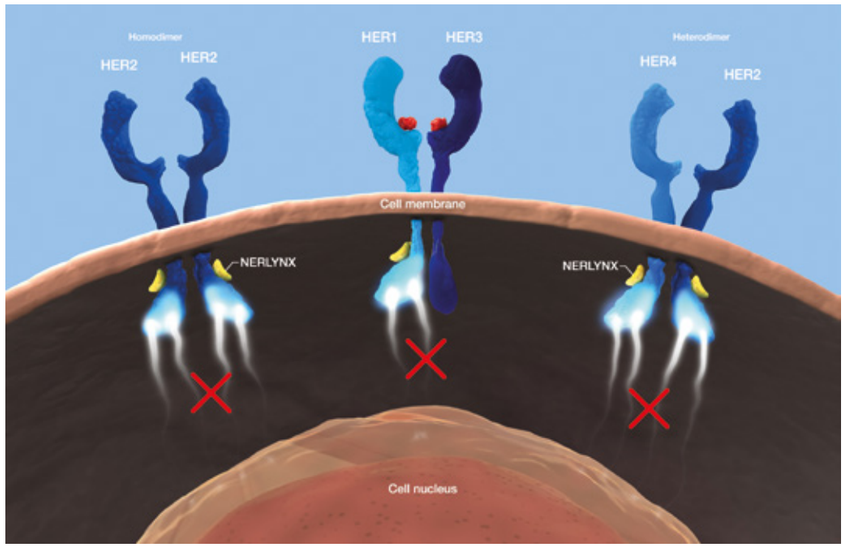


1.2 How does NERLYNX work?

NERLYNX is a tyrosine kinase inhibitor (TKI) that penetrates the cell membrane to target the intracellular domain of the HER receptors, HER1, HER2 and HER4.[7,8]

As a targeted therapy, NERLYNX limits damage to healthy cells, as its activity is focused on the receptors involved in HER2+ breast cancer.[7,8]

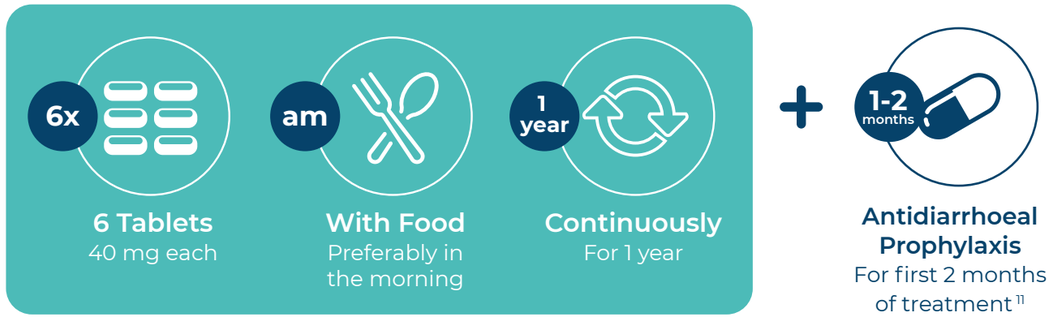
NERLYNX irreversibly binds to the tyrosine kinase domains of HER receptors, resulting in pan-HER signalling inhibition. The sustained inhibition of the HER2 downstream signalling inhibits tumour cell proliferation and increases cell death.[7–11]



2 NERLYNX ADMINISTRATION

2.1 General population

NERLYNX is an oral, once-daily therapy[1]



NERLYNX does not require any special temperature storage conditions.[1]

NERLYNX is to be taken at approximately the same time, preferably in the morning, every day.[1]

If a dose is missed or vomited, NERLYNX is to be resumed the next day.[1]

Tablets should be swallowed whole, and should not be crushed or dissolved.[1]

Grapefruit and pomegranate in any form should be avoided.[1]

2.2 Specific populations

Dose adjustments

Elderly[1]

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

Renal impairment[1]

- No dose adjustment is required for patients with mild to moderate renal impairment.
- NERLYNX has not been studied in patients with severe renal impairment (eGFR ≤29 mL/min/1.73 m^2) including patients on dialysis. Treatment is not recommended.

Hepatic impairment[1]

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

Child-Pugh score[1,2]

Variable	Points		
	1	2	3
Hepatic encephalopathy	None	Stage I-II	Stage III-IV
Acites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds)	<4	4-6	>6

Prognostic sub-group[1,2]

Sum of points	5-6	7-9	10-15
Class	A (mild)	B (moderate)	C (severe)

Pregnancy, lactation & contraception[1]

There are no data from the use of NERLYNX in pregnant women, therefore, NERLYNX should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures while taking NERLYNX and for 1 month after stopping treatment.[1]

It is not known whether NERLYNX 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 NERLYNX.[1]

eGFR, estimated glomerular filtration rate.

3 ADVERSE EVENTS MANAGEMENT[1]

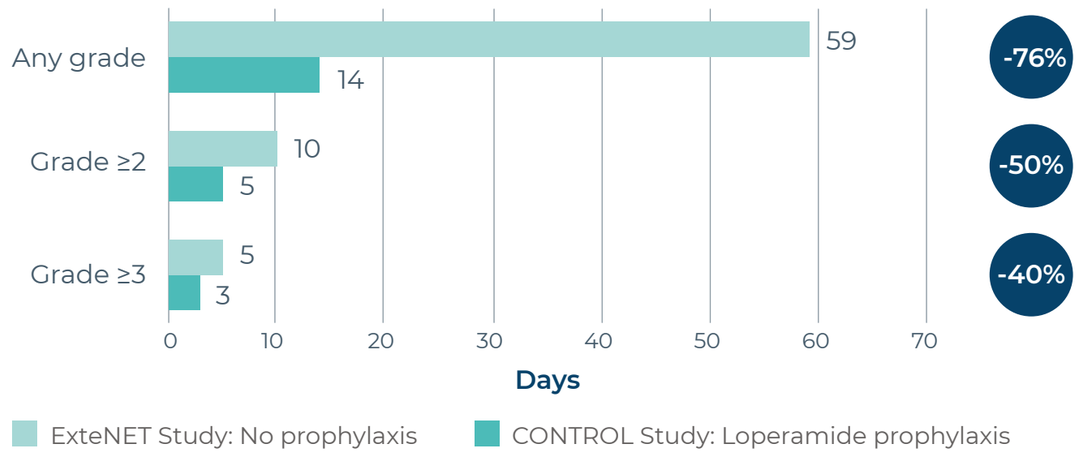
3.1 Adverse events[1]

System organ class	Adverse reaction	All grades (%)	≥ Grade 3 (%)
General disorders	Fatigue	27.3	-
Metabolic and nutritional disorders	Decreased appetite	13.7	-
Hepatobiliary disorders	ALT increase	8.5	1.3
	AST increase	7.4	0.7
Gastrointestinal disorders	Diarrhoea	93.6	37.1
	Nausea	42.5	-
	Abdominal pain*	35.9	-
	Vomiting	26.8	3.5
	Stomatitis	11.2	-
Skin and subcutaneous tissue disorders	Rash	15.4	0.4
	Nail disorders	7.8	0.2
Musculoskeletal and connective tissue disorders	Muscle spasms	10.0	-

Table adapted from Nerlynx SmPC.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Includes abdominal pain and abdominal pain upper.

The addition of antidiarrhoeal prophylaxis to NERLYNX treatment decreased the severity and duration of diarrhoea.[13,14]

Median cumulative duration of diarrhoea (days) for the whole treatment period[13]



3.2 Recommended dose adjustments for adverse event management

Management of some adverse reactions may require dose interruption and/or dose reduction. Adjusting daily dose can improve tolerability and adherence.[1,14]

Recommended Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
6 Tablets (40 mg)	5 Tablets (40 mg)	4 Tablets (40 mg)	3 Tablets (40 mg)
Once Daily Dose **240 mg**	Once Daily Dose **200 mg**	Once Daily Dose **160 mg**	Once Daily Dose **120 mg**

Management according to the severity of adverse reactions and based on individual safety and tolerability[1]

General adverse events[1]
(See pages 8 and 10 for specific management of diarrhoea and hepatotoxicity.)

- **Grade 2** if the patient cannot tolerate → REDUCE NERLYNX treatment dose → Patients unable to tolerate 120 mg daily → PERMANENTLY DISCONTINUE NERLYNX treatment
- **Grade 3** → INTERRUPT NERLYNX treatment
  - Recovery to Grade ≤ 1 or baseline within 3 weeks → RESUME NERLYNX at the next lower dose level
  - Fail to recover within 3 weeks → PERMANENTLY DISCONTINUE NERLYNX treatment
- **Grade 4**
- **Toxicities that result in a treatment delay >3 weeks**
- **Patients that are unable to tolerate 120 mg daily** → PERMANENTLY DISCONTINUE NERLYNX treatment

4 PROACTIVE MANAGEMENT OF DIARRHOEA

4.1 Antidiarrhoeal prophylaxis while on NERLYNX [1,14]

Start your patients on antidiarrhoeal prophylaxis with the first dose of NERLYNX and continue for the first 1-2 months of NERLYNX therapy to decrease the severity, incidence and duration of diarrhoea.[1,14]

Diarrhoea management with loperamide[14]

Time on NERLYNX	Loperamide dose	Frequency
Weeks 1–2 (days 1–14)	4 mg	Three times daily
Weeks 3–8 (days 15–56)	4 mg	Twice daily
Weeks 9–52 (days 57–365)	4 mg	As needed (not to exceed 16 mg per day)

nerlynx® (neratinib) **240 mg** (or as prescribed) (six 40 mg tablets) **1 x daily for 1 year**

DAYS 1 — 14 — 28 — 56 — 365

Proposed example of prophylaxis with loperamide

- 2 mg 2 mg — **4 mg** (two 2 mg capsules) **3 x daily**
- 2 mg 2 mg — **4 mg** (two 2 mg capsules) **2 x daily**
- **4 mg** (two 2 mg capsules) **As needed** (not to exceed 16 mg/day)

Continue loperamide for the first 1-2 months

Adjust loperamide as needed

4.2 Management according to the severity of diarrhoea[15]

The overall management of diarrhoea is based upon its grade as measured by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).[15]

NCI CTCAE: Grading for diarrhoea[15]	
Grade 1	**Increase of <4 stools per day over baseline** Mild increase in ostomy output compared to baseline
Grade 2	**Increase of 4-6 stools per day over baseline** Moderate increase in ostomy output compared to baseline
Grade 3	**Increase of ≥7 stools per day over baseline** Incontinence, hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living (ADL)
Grade 4	**Life threatening consequences** Urgent intervention indicated

Dose adjustements according to the severity of diarrhoea and based on individual safety and tolerability[14]

- Grade 1 diarrhoea
- Grade 2 diarrhoea lasting <5 days
- Grade 3 diarrhoea lasting <2 days

→ Diet modifications
- Fluid intake of ~2L should be maintained to avoid dehydration

→ **ADJUST** antidiarrhoeal treatment dose

→ Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration

- Any grade with complicated features*
- Grade 2 diarrhoea lasting ≥5 days†
- Grade 3 diarrhoea lasting >2 days†

→ Diet modifications
- Fluid intake of ~2L should be maintained to avoid dehydration

→ **INTERRUPT** NERLYNX treatment

→ Diarrhoea resolves to Grade 0–1 in ≤1 week → **RESUME** NERLYNX at the same dose

→ Diarrhoea resolves to Grade 0–1 in >1 week → **RESUME** NERLYNX at the next lower dose level

→ Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration

- Grade 4 diarrhoea
- Grade 3 diarrhoea persists > 3 weeks
- Diarrhoea recurs to Grade 2 or higher at 120 mg per day
- Patients that are unable to tolerate 120 mg

→ **PERMANENTLY DISCONTINUE** NERLYNX treatment

*Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia.
†Despite being treated with optimal medical therapy.

4.3 Helpful advice

Diet modifications

Patients should be instructed to adapt their diet in order to minimise diarrhoea.[16,17]

Things to do:

Eat small, more frequent meals

Drink 8 to 10 large glasses (a total of ~2 liters) of clear liquids every day

Choose foods that are easy to digest (low-residue diet)

These include bananas, rice, applesauce and toast

Things to avoid:

Medicines such as laxatives or stool softeners

Caffeine, alcohol, dairy, fat, fibre, orange juice, grapefruit juice, pomegranate juice, prune juice, and spicy foods

Support materials

There are numbers of materials available for you and your patients to help support them throughout their treatment with NERLYNX:

The Health Care Professional Brochure, with information on measures to help reduce side effects.

The Patient Brochure and the Patient Treatment Guide, providing education to help prepare for treatment.

The Patient Treatment Diary, to monitor their daily symptoms, enabling treatment adjustments as needed.

5 MANAGEMENT OF HEPATOTOXICITY[1]

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.[1]

Dose modifications for hepatotoxicity[1]

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 lowest 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 • 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

6 CONTRAINDICATIONS[1]

- Hypersensitivity to the active substance or to any of the excipients: mannitol (E421), microcrystalline cellulose, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogrol, talc, iron oxide red (E172).
- Severe hepatic impairment (Child-Pugh C).

Other medicines

Contraindicated	Examples
Co-administration with strong inducers of the CYP3A4/Pgp isoform of cytochrome P450	• carbamazepine, phenytoin (antiepileptics) • St John's wort (*Hypericum perforatum*) (herbal product) • rifampicin (antimycobacterial)

7 INTERACTIONS[1]

Medications	Considerations	Examples
Proton pump inhibitors, H2-receptor antagonists and antacids	Co-administration with proton pump inhibitors (PPIs) is not recommended. If H2-receptor antagonists are used: NERLYNX should be taken at least 2 hours before or 10 hours after the intake of the H2-receptor antagonist. If antacids are taken: separate the dosing of NERLYNX and the antacid by at least 3 hours.	omeprazole, lansoprazole, dexpansoprazole, rabeprazole, pantoprazole; nizatidine, famotidine, cimetidine or ranitidine
Strong or moderate CYP3A4/P-gp inhibitors	Concomitant treatment is not recommended due to risk of increased exposure to NERLYNX. If the inhibitor cannot be avoided, reduce NERLYNX dose.	atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and voriconazole, grapefruit/ pomegranate or grapefruit/ pomegranate products
Moderate CYP3A4/P-gp inducers	Concurrent use of NERLYNX with moderate CYP3A4/P-gp is not recommended as it may lead to loss of efficacy.	bosentan, efavirenz, etravirine, phenobarbital, primidone or dexamethasone
Strong CYP3A4/P-gp inducers	Concurrent use with NERLYNX is contraindicated.	phenytoin, carbamazepine, rifampicin, or herbal preparations containing St John's Wort *(Hypericum perforatum)*
Breast cancer resistance protein efflux transporters	NERLYNX may inhibit breast cancer resistance protein (BCRP) intestinal level as suggested by in vitro studies. Clinical studies with BCRP substrates have not been conducted. Patients who are treated with BCRP substrates should be monitored carefully.	rosuvastatin, sulfasalazine or irinotecan
P-glycoprotein efflux transporters	In in-vitro studies, NERLYNX is an inhibitor of P-glycoprotein (P-gp) efflux transporters. 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. These patients should be carefully monitored.	digoxin, colchicine, dabigatran, phenytoin, statins, cyclosporine, everolimus, sirolimus or tacrolimus

8 PATIENT DIALOGUE IS KEY[18]

By integrating NERLYNX into your patients' treatment plan from the start, and explaining the importance of adherence, you can help your patient stick to their treatment and reduce their risk of recurrence.

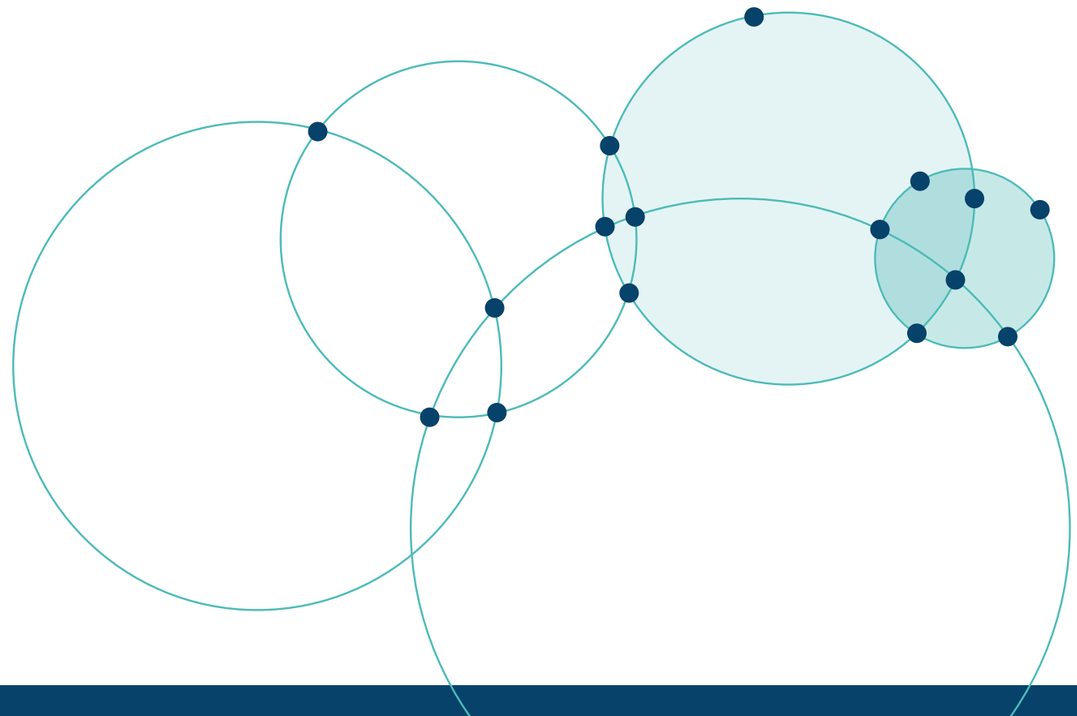
Your support helps patients to be:[18]

More informed

More prepared

More supported

Make sure that you provide your patients with the Risk Management Plan (RMP) educational materials to help them to understand more about their treatment and how to be aware of, and minimise the risk of adverse events.



nerlynx® ▼
(neratinib)

NERLYNX ABBREVIATED PRESCRIBING INFORMATION

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.
See below for how to report any adverse events.

NAME OF THE MEDICINAL PRODUCT: Nerlynx 40 mg film-coated tablets.

CLINICAL PARTICULARS: **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.

Posology and method of administration: Nerlynx treatment should be initiated and supervised by a physician experienced in the administration of anticancer 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 modification: Nerlynx dose modification is recommended based on individual safety and tolerability. The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (For complete information, please refer to SmPC Section 4.2.)

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 SmPC Section 5.2).

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1. Co-administration with strong inducers of the CYP3A4/Pgp isoform of cytochrome P450: Carbamazepine, phenytoin (antiepileptics), St John's wort (*Hypericum perforatum*) (herbal product), Rifampicin (antimycobacterial). Severe hepatic impairment (Child-Pugh C)(see section 5.2).

Special warnings and precautions for use: Diarrhoea. Patients with a significant chronic gastrointestinal disorder. Elderly patients. Patient with Renal impairment. Liver dysfunction. Left ventricular dysfunction. Pregnancy. Patients with symptomatic skin and subcutaneous tissue disorders. For complete information, please refer to SmPC Section 4.4.

Interaction with other medicinal products and other forms of interaction: Concomitant use of strong or moderate CYP3A4/Pgp inhibitors significantly increase neratinib exposure. CYP3A4/Pgp inducers significantly decrease neratinib exposure. Grapefruit/pomegranate or grapefruit/pomegranate juice should be avoided. For complete information, please refer to SmPC Section 4.5.

Contraceptives and breastfeeding: Women of child-bearing potential must use highly effective contraceptive measures while taking Nerlynx and for 1 month after stopping treatment. Men should use a barrier method of contraception during treatment and for 3 months after stopping treatment. It is not known whether Nerlynx is excreted in human milk. A risk to the breast-fed infant cannot be excluded. For complete information, please refer to SmPC Section 4.6.

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%). For complete information, please refer to SmPC Section 4.8.

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. For complete information, please refer to SmPC Section 4.9.

MARKETING AUTHORISATION HOLDER : Pierre Fabre Médicament - 45, place Abel Gance, 92100 Boulogne- Billancourt, France.

DATE OF REVISION OF THE TEXT: June 2020. Detailed information on this medicinal product is available on the website of the European Medicines Agency http:// www.ema.europa.eu.
For complete information, please refer to SmPC. Latest review of EU SmPC : 25/06/2020.

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 requested to report any suspected adverse reactions via the national reporting system (Appendix V - European Medicines Agency - Europa EU) and/or to the Pharmacovigilance department of Pierre Fabre laboratories (www.pierre-fabre.com/en/pharmacovigilance)

Please download the Summary of Products characteristics by using this QR Code

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