nerlynx®
(neratinib)

PHARMACIST / NURSE GUIDE

This guide is conceived in order to best accompany your patients treated with NERLYNX for early-stage hormone receptor positive, HER2-overexpressed/amplified breast cancer, who completed adjuvant trastuzumab-based therapy less than one year ago.

▼ 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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CONTENTS

References:

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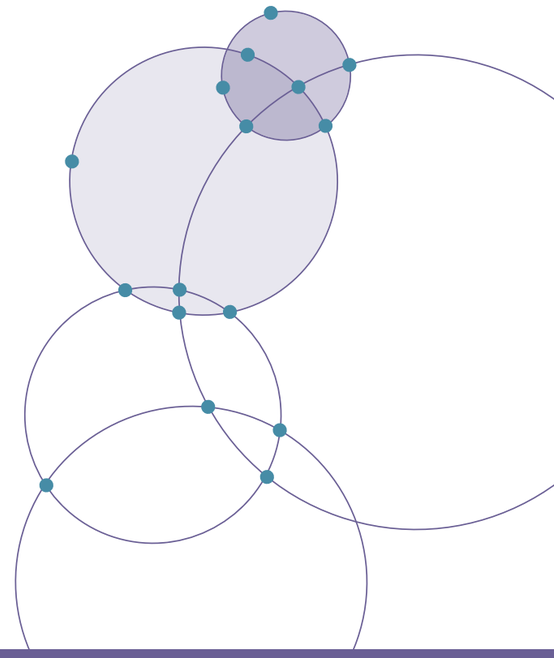


1 PATHOLOGY & TREATMENT

HER2+ Breast Cancer

HER2+ breast cancer is a form of the disease in which cells test positive for a protein called Human Epidermal growth factor Receptor 2 – or HER2 for short. HER2 receptors are proteins found on the surface of cells in the body. They help to control how healthy breast cells grow, divide and repair themselves. However, sometimes the gene that controls the HER2 protein goes wrong, and the cells have a larger number of HER2 receptors on their surface than usual. This results in cells dividing and growing faster than normal.

HR+ Breast Cancer

Some breast cancers are fueled by estrogen and/or progesterone, which are natural female hormones. Breast cancer cells may have estrogen receptors (ER) and/or progesterone receptors (PR) that 'catch' these hormones. Breast cancers of this type are termed hormone receptor positive – or HR+ for short.

Epidemiology

Amplification or overexpression of HER2 occurs in approximately 15–30% of breast cancers.[1]

Around 80% of breast cancers test positive for ER, with 65% of these also testing positive for PR.[2]

Around 10% of breast cancers are HER2+/HR+.[3]

Medicinal treatments

To treat HER2+/HR+ breast cancer, several treatments exist:

- Chemotherapy
- Endocrine therapy which can block the body's ability to produce hormones and/or interfere with the action of hormones, slowing or stopping the growth of hormone-sensitive tumors.[4]
- Targeted therapies using drugs to identify and attack specific types of cancer cells with less harm to normal cells.

NERLYNX is a HER2-targeted therapy which specifically targets HER2+ cancer cells.

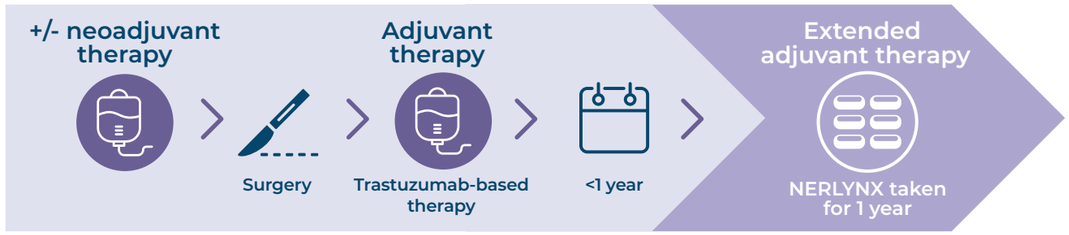
Concept of adjuvant therapy

After surgery, an adjuvant therapy is delivered to destroy remaining cancer cells. For HER2+/HR+ breast cancer patients, the targeted therapy is a trastuzumab-based therapy. When adding NERLYNX after trastuzumab-based therapy, it is considered as an extended adjuvant therapy. The goal of an extended adjuvant therapy is to reduce risk of recurrence.

2 INDICATION

NERLYNX is indicated for the extended adjuvant treatment of adult patients with early-stage breast cancer [5]

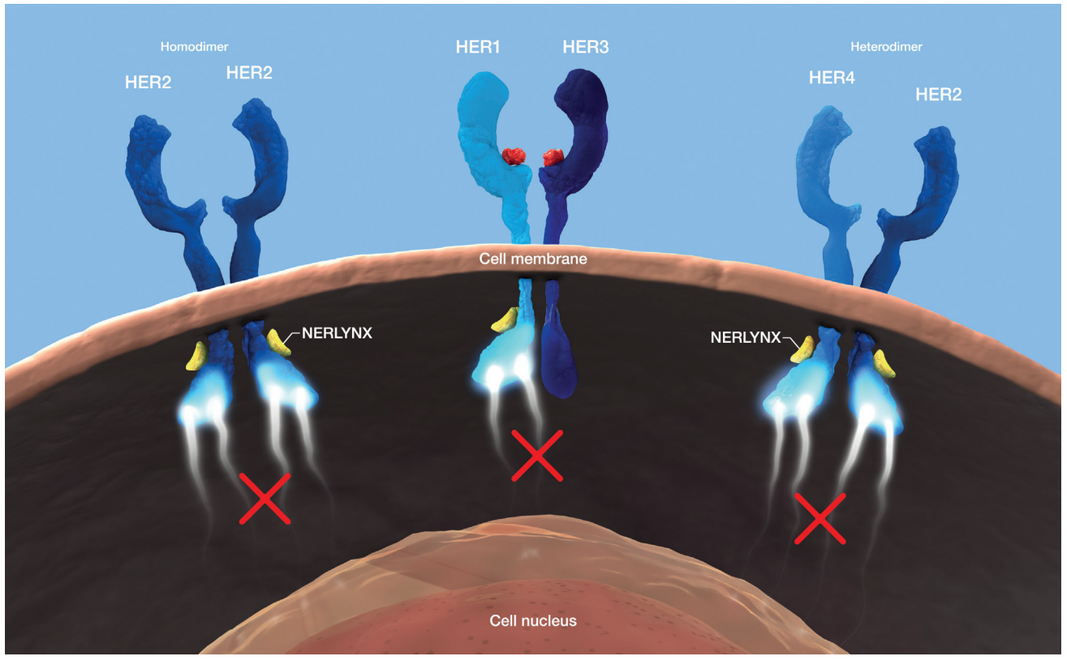
- HER2-overexpressed/amplified
- Hormone receptor positive
- And who completed adjuvant trastuzumab-based therapy less than one year ago.



3 MECHANISM OF ACTION

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. [6,7]

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 tumor cell proliferation and increases cell death. [6-10]



4 POSOLOGY & ADMINISTRATION

General population

NERLYNX is an oral, once-daily therapy[5]

6x — **6 Tablets**
40 mg each

am — **With Food**
Preferably in the morning

1 year — **Continuously**
For 1 year

\+

1-2 months — **Antidiarrhoeal Prophylaxis**
For first 2 months of treatment [11]

NERLYNX is to be taken at approximately the same time, preferably in the morning, every day.[5]

If a dose is missed or vomited, NERLYNX is to be resumed the next day.[5]

Tablets should be swallowed whole, and should not be crushed or dissolved.[5]

Grapefruit and pomegranate in any form should be avoided.[5]

5 PRESCRIBING CONDITIONS

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

NERLYNX is dispensed in community pharmacies.

6 PACKAGING & STORING

180 tablets for 1 month of treatment

Standard Dosing 240 mg each day

40 mg — 4.3mm 40 mg Tablets

10.5mm

NERLYNX does not require any special temperature storage conditions.[5]

- NERLYNX comes as film-coated tablets containing an active substance called neratinib.
- Each film-coated tablet contains neratinib maleate, equivalent to 40 mg neratinib.
- NERLYNX tablets are packaged in a white plastic bottle, with a child-resistant cap and a foil tamper-evident seal.
- Each bottle contains 180 film-coated tablets, for 30 days' treatment.
- The film-coated tablets are red and oval shaped: 'W104' is on one side and the other side is plain.
- A canister containing 1 g silica gel is enclosed with the tablets in each bottle, to keep them dry. Do not swallow the silica gel.
- Keep the bottle tighly closed in order to protect from moisture.
- Shelf life : 3 years.[12]

LIST OF EXCIPIENTS [12]

Tablet core

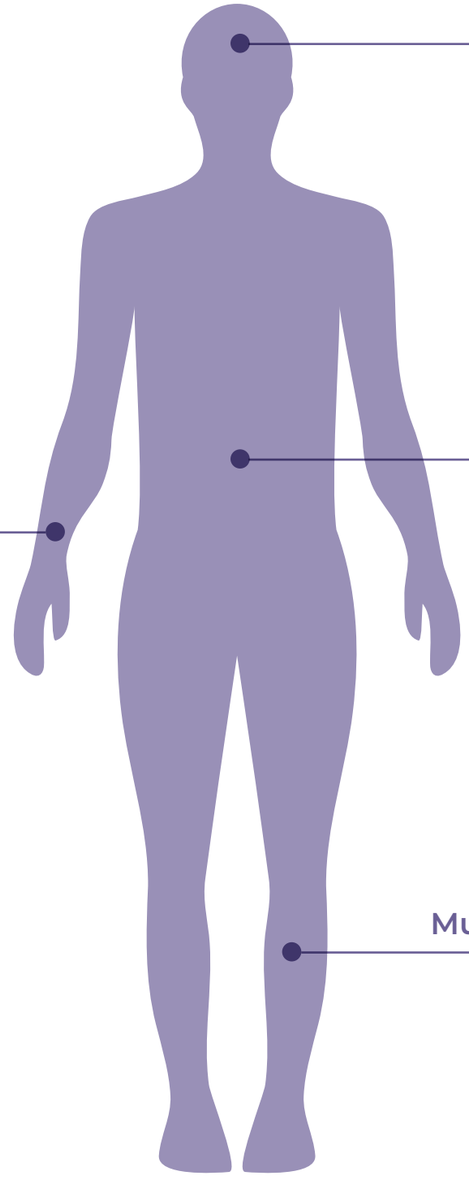
- Mannitol (E421)
- Microcrystalline cellulose
- Crospovidone
- Povidone
- Silica, colloidal anhydrous
- Magnesium stearate

Tablet coating

- Polyvinyl alcohol
- Titanium dioxide (E171)
- Macrogol
- Talc
- Iron oxide red (E172)

7 ADVERSE EVENTS

Side effects mostly reported with NERLYNX[5]:



Fatigue (27.3%)

Skin and subcutaneous tissue disorders

- Rash (15.4%)

Gastrointestinal disorders

- Diarrhoea (93.6%)
- Nausea (42.5%)
- Adbominal pain (22.7%) + upper (13.2%)
- Vomiting (26.8%)
- Stomatitis (11.2%)
- Decreased appetite (13.7%)

Muscle spasm (10.0%)

Patients may also experience side effects related to associated treatment, as hormonotherapy.

8 DOSE ADJUSTEMENTS

For general adverse events

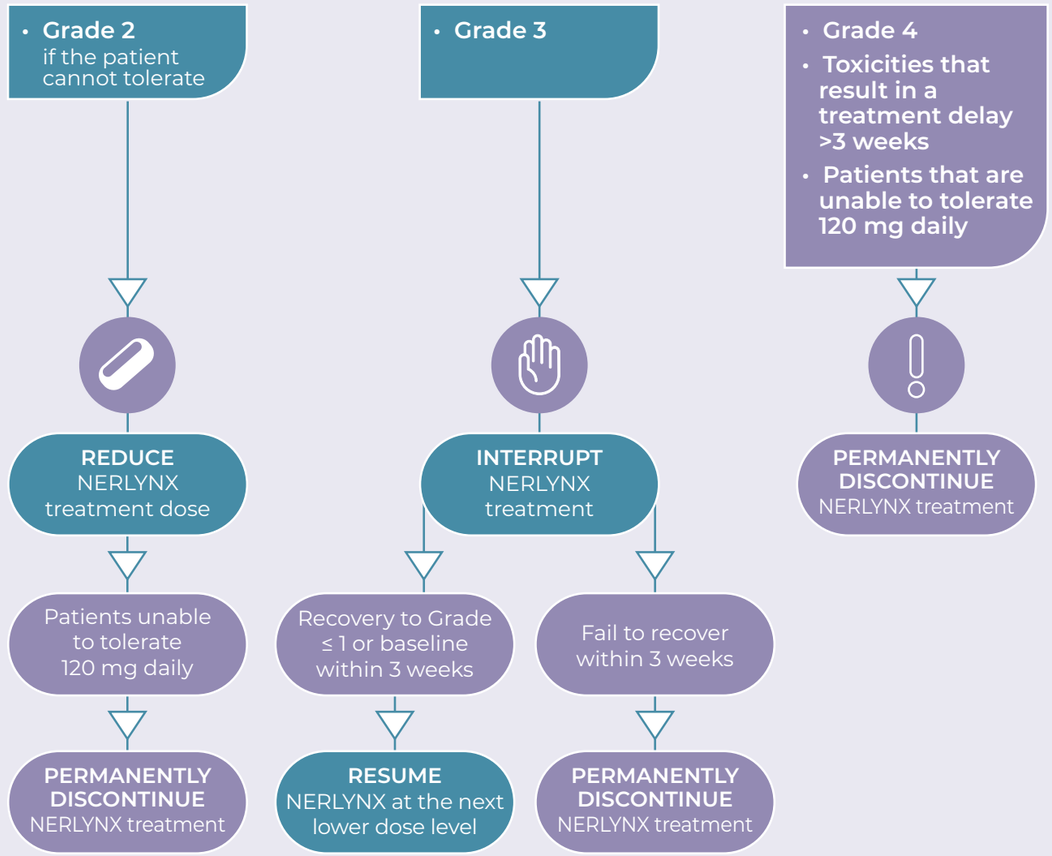
Management of some adverse reactions may require dose interruption and/or dose reduction. Adjusting daily dose can improve tolerability and adherence.[5,11]

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 [5]

General adverse events[5]

(See pages 9 and 10 for specific management of hepatotoxicity and diarrhoea.)



Specific populations

Elderly[5]

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

Renal impairment[5]

- 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[5]

- 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[13]

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[13]

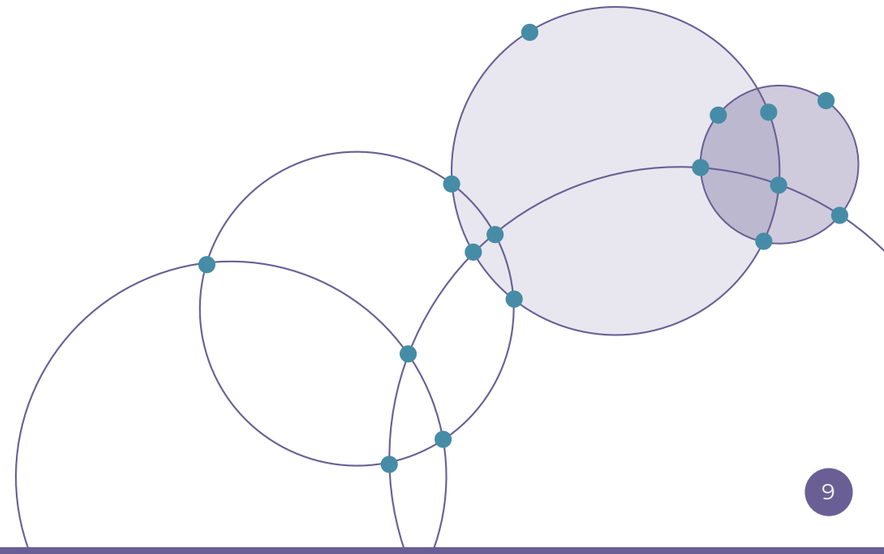
Sum of points	5-6	7-9	10-15
Class	A (mild)	B (moderate)	C (severe)

For general Hepatotoxicity

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.[5]

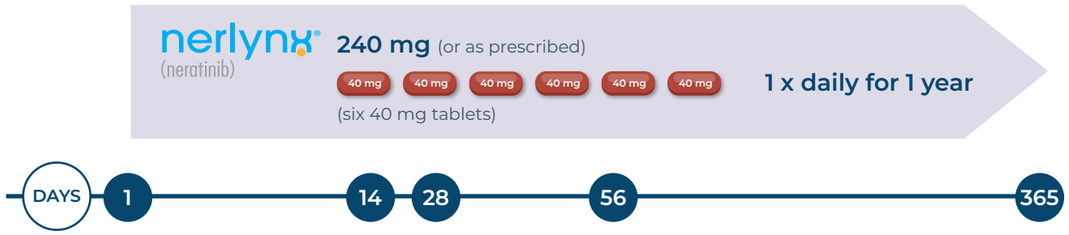
Severity of hepatotoxicity*	Action
• Grade 3 ALT (>5-20 x ULN) OR • Grade 3 bilirubin (>3-10 x ULN)	• Stop NERLYNX until recovery to Grade 0-1 • Evaluate alternative causes • Resume NERLYNX at the next lowest level if recovery to Grade 0-1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again 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 v5.0

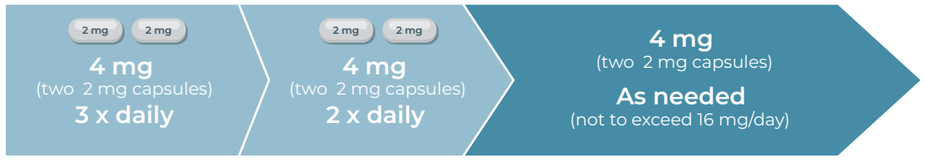


Antidiarrhoeal prophylaxis while on NERLYNX

Diarrhoea due to NERLYNX treatment, the most common adverse reaction of any grade (93.6%), must be monitored. The addition of antidiarrhoeal prophylaxis with the first dose of NERLYNX and during the first 1-2 months of NERLYNX therapy decreases the severity, incidence and duration of diarrhoea.[5, 11]



Proposed example of prophylaxis with loperamide

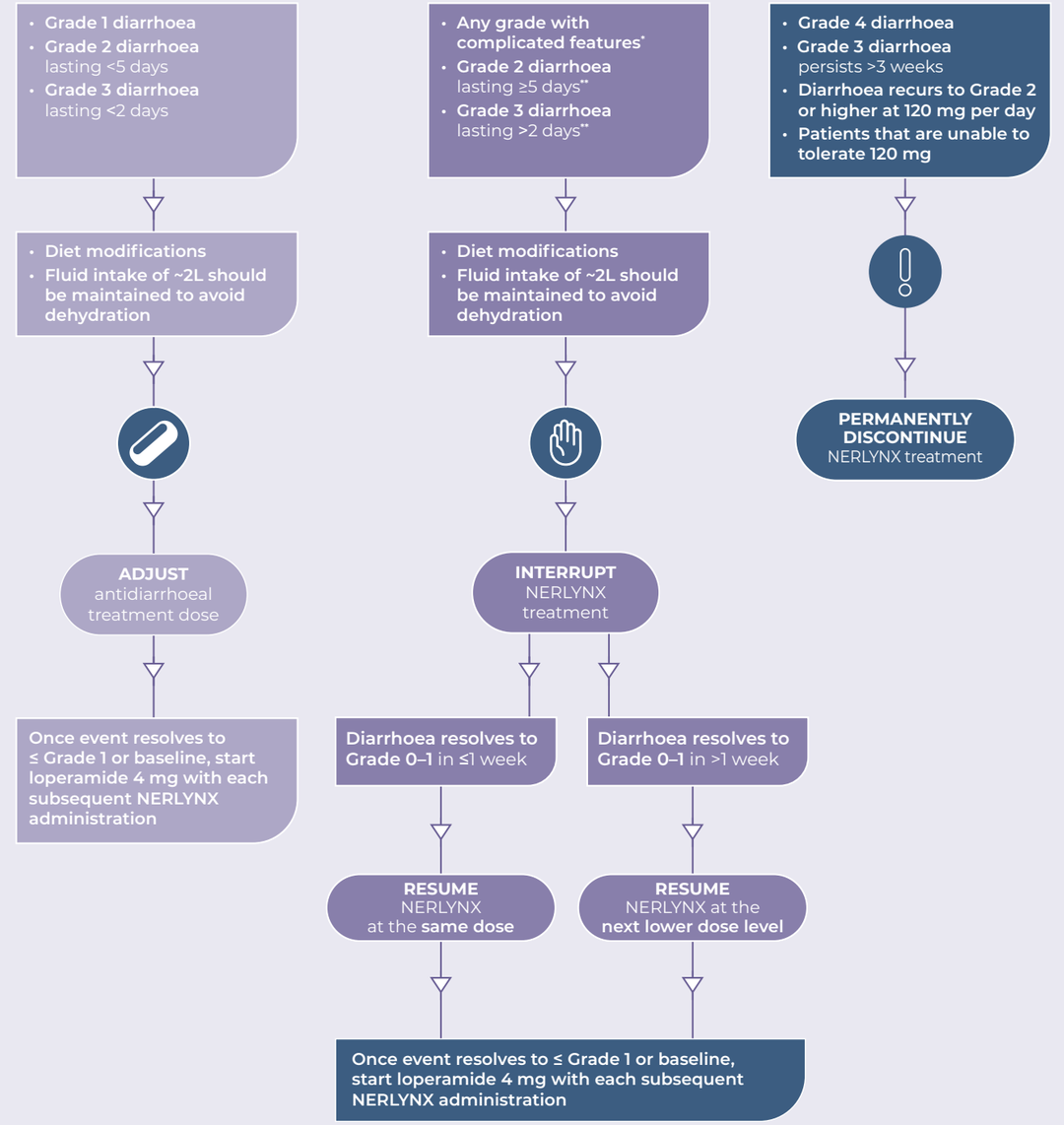


Management according to the severity of diarrhoea[14]

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).[14]

NCI CTCAE: Grading for diarrhoea[14]	
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[11]



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

Diet modifications [15,16]

Diet plays an important role in the treatment success with NERLYNX because some foods may impact how your patients feel after taking NERLYNX. It is important to have a proactive discussion about diet modifications.

Things to do:

NERLYNX should be taken with food, preferably in the morning every day.

Eat small, more frequent meals

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

Choose more bland foods (like the BRAT diet: bananas, rice, applesauce, toast)

Choose foods that are low in fiber and high in protein and potassium

Things to avoid:

Medicines such as laxatives or stool softeners

Dairy products (except for yogurt)

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

Do not chew, crush, or split tablets

Contraindications [5]

- 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)

Overdose [5]

- 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.

Pregnancy, contraception & breast-feeding [5]

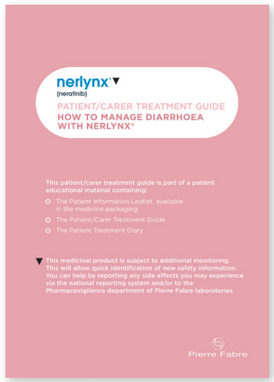
- There are no data from the use of NERLYNX in pregnant women, therefore, NERLYNX should not be used during pregnancy unless the clinical condition of the woman requires treatment with neratinib. If neratinib is used during pregnancy, or if the patient becomes pregnant while taking NERLYNX, the patient should be informed of the potential hazard to the foetus.
- 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.
- 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.

Interactions [5]

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, lopinavir, ketoconazole, itraconazole, clarithromycin, troleandomycin, voriconazole, cobicistat, ciprofloxacin, cyclosporin, diltiazem, fluconazole, erythromycin, fluvoxamine or verapamil
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

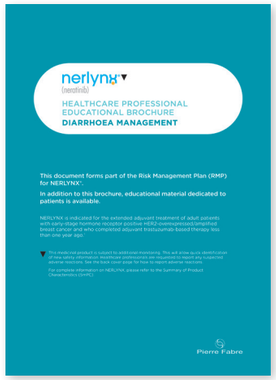
There are numbers of materials available for you and your patients to help support them throughout their treatment with NERLYNX:

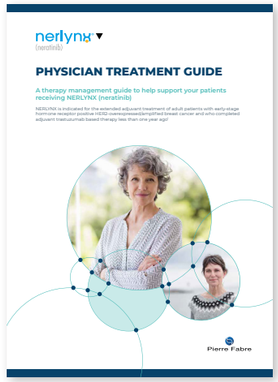
The Patient Brochure and the Patient Treatment Guide, providing education to help prepare for treatment.



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

The Health Care Professional Brochure and the Physician Treatment Guide, with information on measures to help reduce side effects.





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(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.[5]

Administration

NERLYNX is an oral drug, it implies that it will be delivered in community pharmacies and taken by the patients in the comfort of their homes.

Word on efficacy [17]

NERLYNX (neratinib) was studied in a clinical trial of 2,840 women who had early-stage HER2+ breast cancer. The phase 3 trial examined the safety and efficacy of NERLYNX by comparing women who took NERLYNX with those who were given a placebo. These women were followed over time-some for as long as approximately 8 years. Participants were randomly selected to receive NERLYNX and were not told whether they were receiving the medicine or a placebo.

In the clinical trial, within the intention-to-treat population, NERLYNX relatively reduced the risk of recurrence by 33% at 2 years and the results were confirmed at 5 years with a 27% reduction in the risk of recurrence.

A greater reduction of the risk of recurrence was found in the HER2+/HR+ population

2 **years**	***5*** **years**
51%	***42%***

At 2 years, in the HER2+/HR+ population subgroup, iDFS = 95.3% in NERLYNX arm (n=671) versus 90.9% in Placebo (n=668).

HER2+ = Human Epidermal growth factor Receptor 2 positive / HR+ = Hormone Receptor positive / iDFS = invasive Disease Free Survival.

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%).[5]

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

Pierre Fabre

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