nerlynx®
(neratinib)

PHARMACIST / NURSE TOOL
HOW TO USE NERLYNX®

This tool 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.

You can help by reporting any side effects you may experience via your national reporting system and/or to the Pharmacovigilance department of Pierre Fabre laboratories (www.pierre-fabre.com/en/pharmacovigilance). This medicinal product is subject to risk minimisation measures.

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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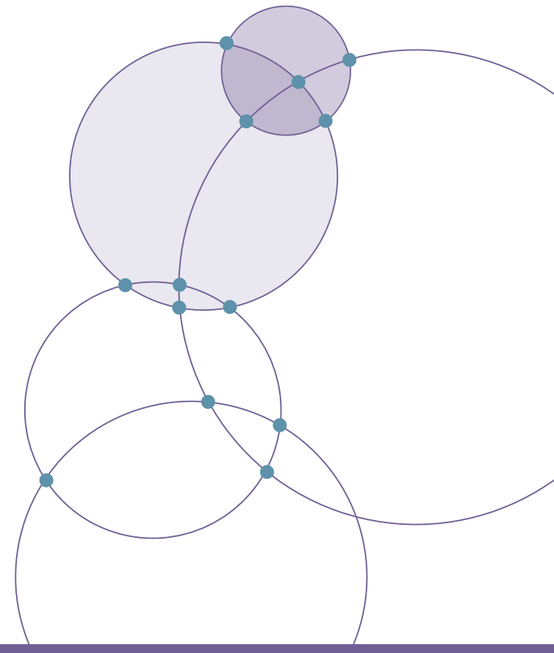


1 PATHOLOGY & TREATMENT

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 (HER2). 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 'capture' these hormones. Breast cancers of this type are termed hormone receptor positive (HR+).

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.

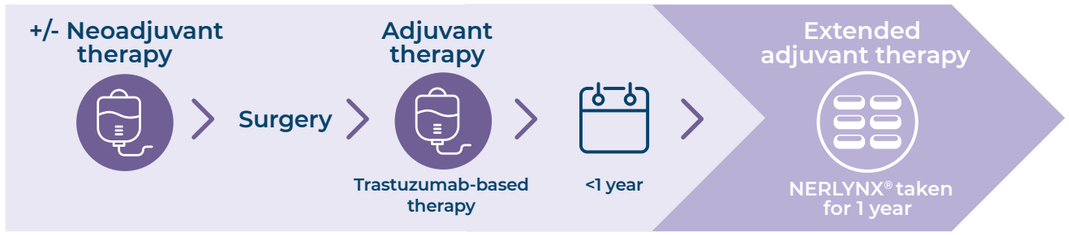
Concept of adjuvant therapy

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]

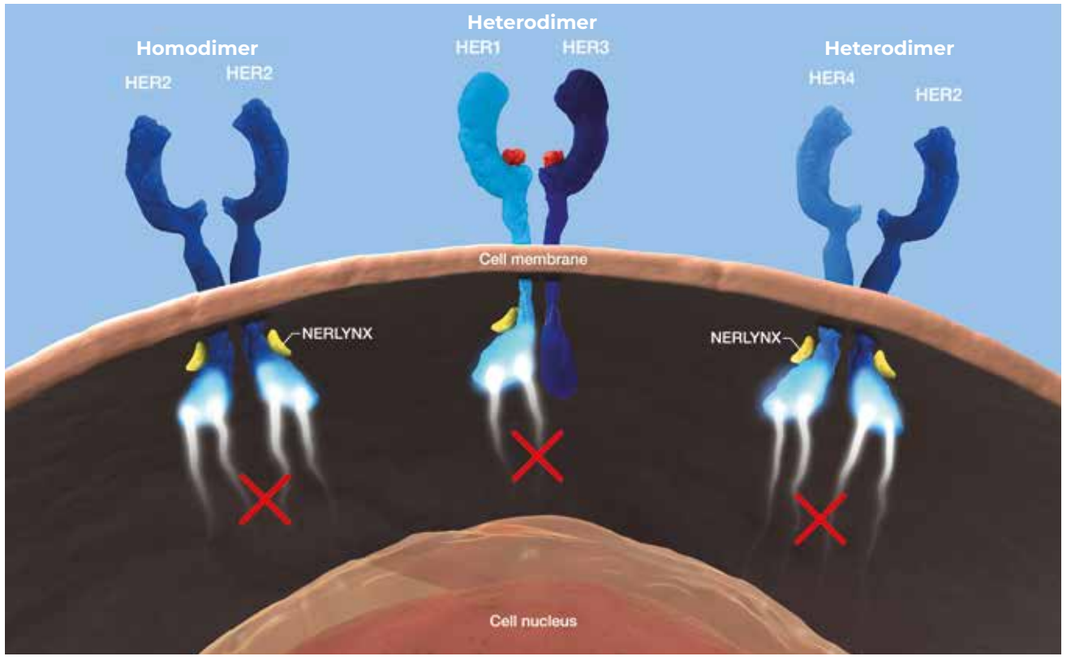
- **HER2-overexpressed/amplified**
- **Hormone receptor positive**
- **And who completed adjuvant trastuzumab-based therapy less than one year ago.**



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® should be initiated within 1 year after completion of adjuvant trastuzumab-based therapy [5]

NERLYNX® should be taken with food, preferably in the morning every day, continuously for 1 year.[5]

If a dose of NERLYNX® is missed or vomited, inform patients that the missed dose should not be replaced and to resume NERLYNX® with the next scheduled daily dose.[5]

Tablets should not be chewed, crushed, dissolved or split prior to swallowing.[5]

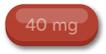
Grapefruit or pomegranate juice may inhibit CYP3A4 and/or P-gp and should be avoided during treatment with NERLYNX®.[5]

5 PRESCRIBING CONDITIONS

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

NERLYNX® can be dispensed in community pharmacies or hospital pharmacies depending on the country.

6 PACKAGING & STORING



4.3mm 40 mg Tablets

10.5mm

180 tablets for 1 month of treatment

Standard Dosing 240 mg each day

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.[11]

LIST OF EXCIPIENTS[11]

Tablet core

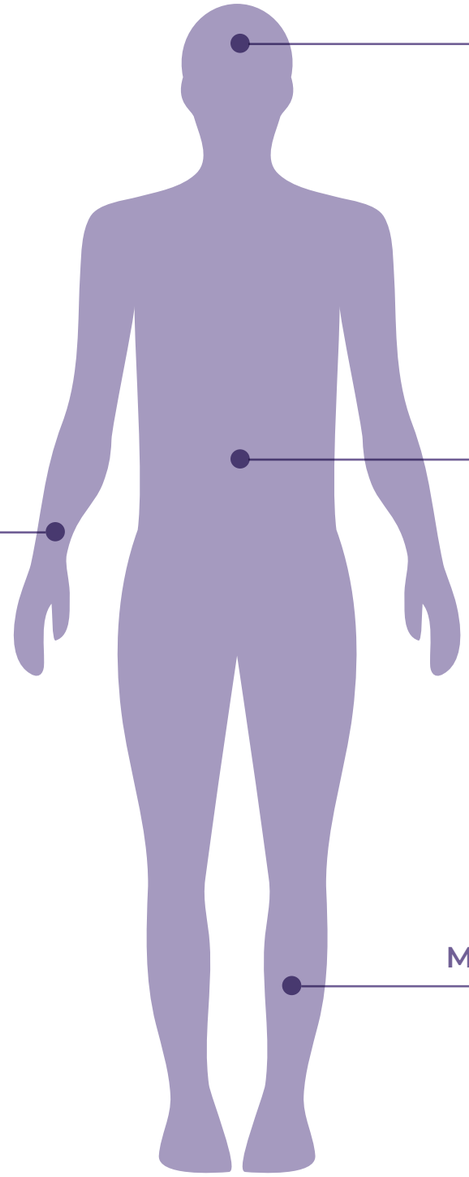
- Mannitol (E421)
- Microcrystalline cellulose
- Crospovidone
- Povidone
- Silica, colloidal anhydrous
- Magnesium stearate

Tablet coating

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

7 ADVERSE REACTIONS

Averse reactions 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 adverse reactions related to associated treatment, as hormonotherapy.

8 DOSE ADJUSTEMENTS

For general adverse reactions

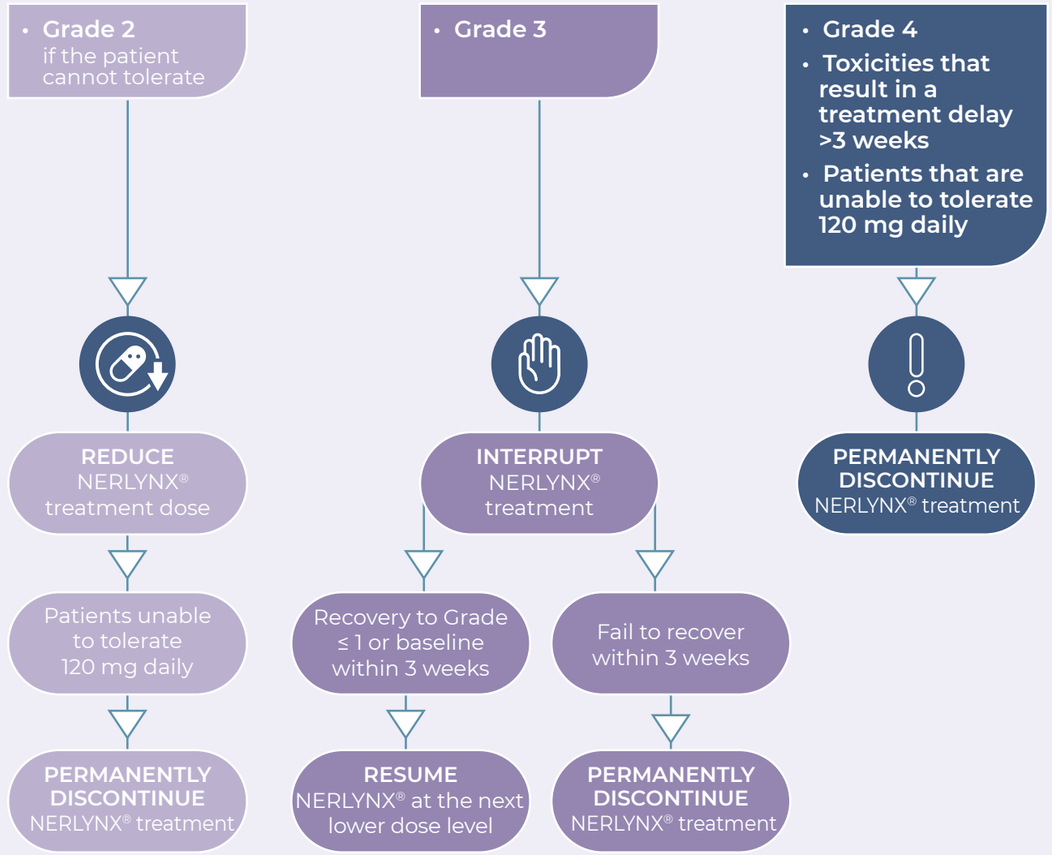
Management of some adverse reactions may require dose interruption and/or dose reduction. Adjusting daily dose can improve tolerability and adherence.[5]

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 patient individual safety and tolerability[5]

General adverse reactions[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).

Child-Pugh score[12]

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[12]

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

For general hepatotoxicity

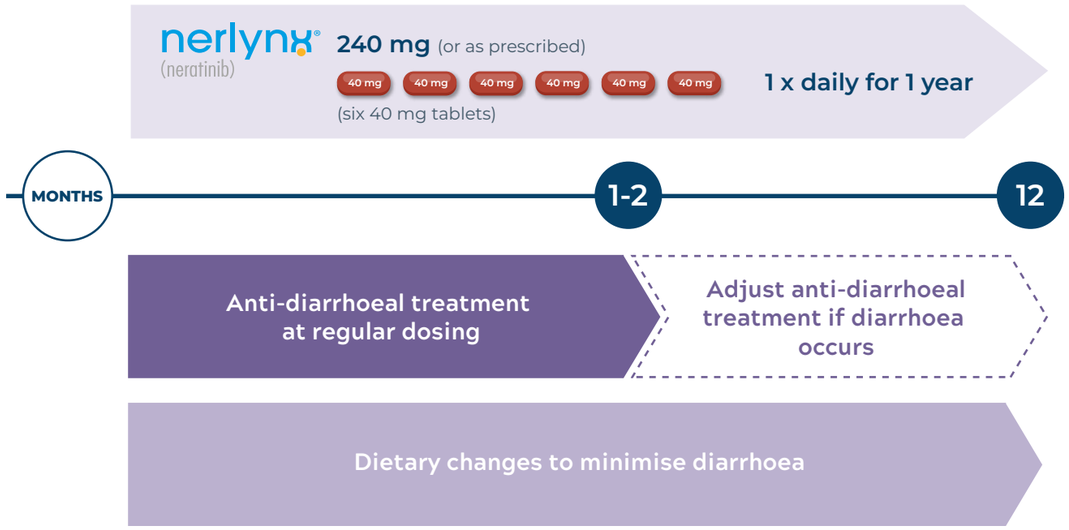
Hepatotoxicity has been reported in patients treated with NERLYNX®. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin should be monitored at 1 week, then monthly for the first 3 months and every 6 weeks thereafter while on treatment or 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 ≤1 • Evaluate alternative causes • Resume NERLYNX® at the next lowest 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 v5.0

Anti-diarrhoeal 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 anti-diarrhoeal 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]

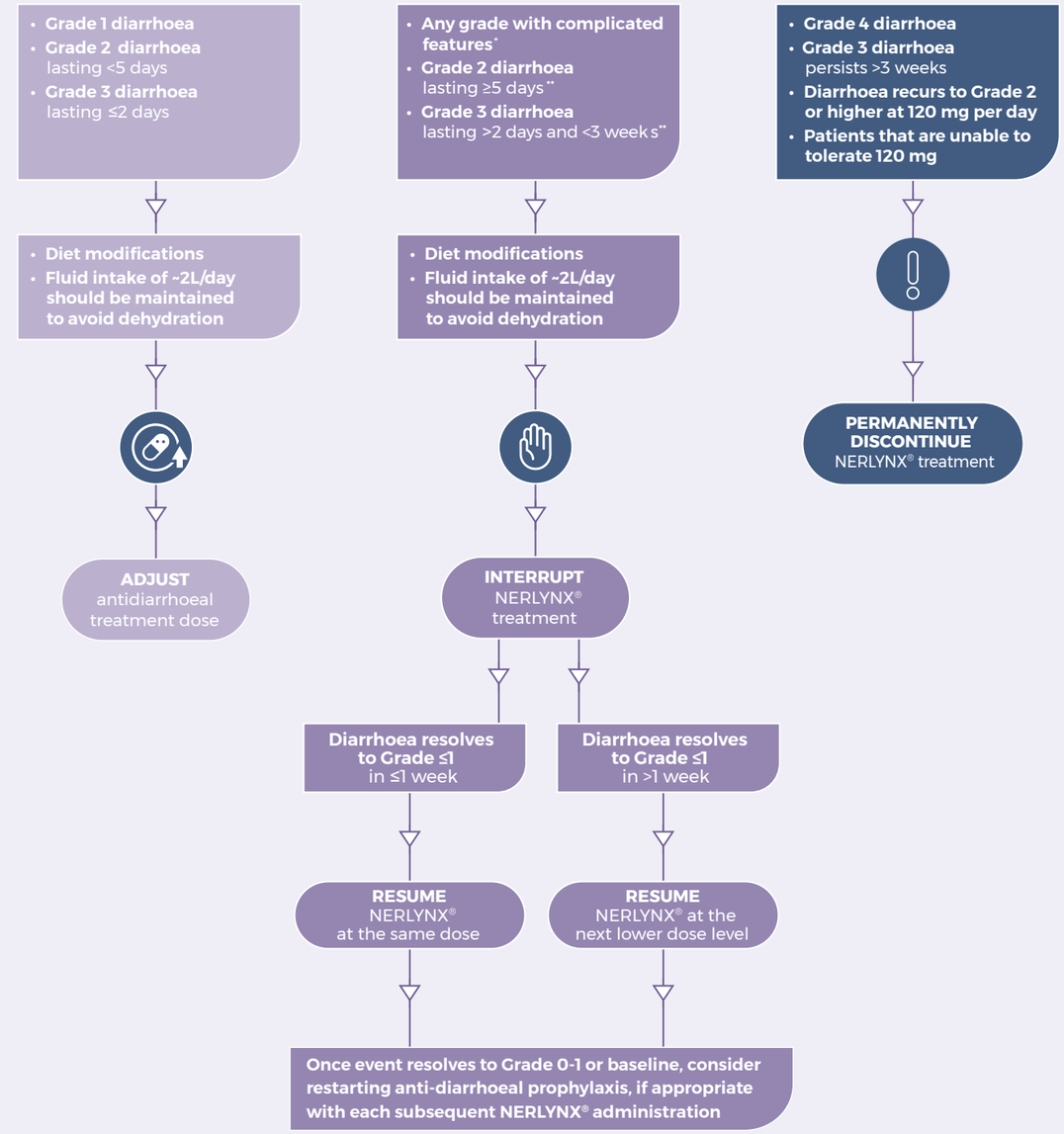


Management according to the severity of diarrhoea[13]

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).[13]

NCI CTCAE: Grading for diarrhoea[13]	
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 patient individual safety and tolerability[5]



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

Dietary changes in the setting of diarrhoea[14,15]

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:

Eat small, frequent meals

Drink more clear liquids

Try to drink ~2L of clear fluids per day. These include water, sports drinks, broth, weak decaffeinated tea, caffeine-free soft drinks, clear juices, and gelatin.

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

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 and/or 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]

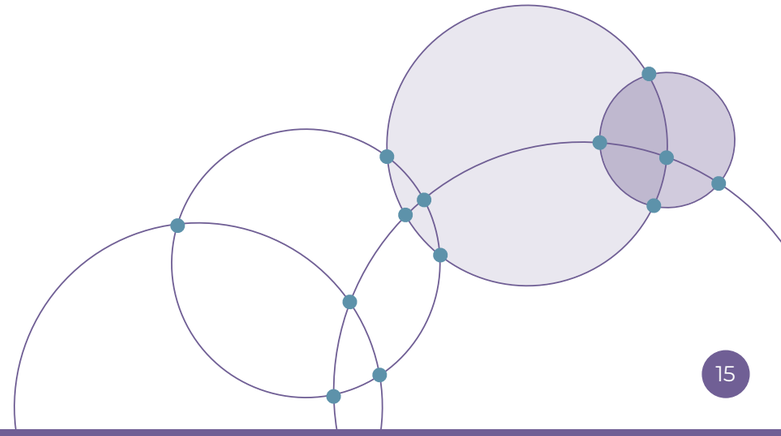
Medications	Considerations	Examples
Proton pump inhibitors, H2-receptor antagonists and antacids	Co-administration with proton pump inhibitors (PPIs) is not recommended. If H2-receptor antagonists are used: NERLYNX® should be taken at least 2 hours before or 10 hours after the intake of the H2-receptor 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®:

EDUCATIONAL MATERIALS FOR DIARRHOEA MANAGEMENT

- **EDUCATIONAL MATERIAL: GUIDE FOR HEALTHCARE PROFESSIONALS ON** DIARRHOEA MANAGEMENT
- **PATIENT/CARER TREATMENT GUIDE** HOW TO MANAGE DIARRHOEA WITH NERLYNX®
- **THE PATIENT TREATMENT JOURNAL**

You can contact your Pierre Fabre local representative or our medical information to get these educational materials, which are specific to each country.



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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.

Brief information on product efficacy[16]

NERLYNX® (neratinib) was studied in a clinical trial of 2,840 women who had early-stage HER2+ breast cancer. The phase III trial examined the safety and efficacy of NERLYNX® by comparing women who took for 12 months NERLYNX® with those who were given a placebo. The randomized patients were followed for 8 years. Participants were randomly selected to receive NERLYNX® and were not told whether they were receiving the medicine or a placebo.

In this 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%**
HR=0.49 [95% CI: 0.30-0.78]	HR=0.58 [95% CI: 0.41-0.82]

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]

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).

For complete information, please refer to : NERLYNX®
Summary of Product Characteristics
https://www.ema.europa.eu/en/documents/product-information/nerlynx-epar-product-information_en.pdf

Pierre Fabre

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