



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.



▼ 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 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.

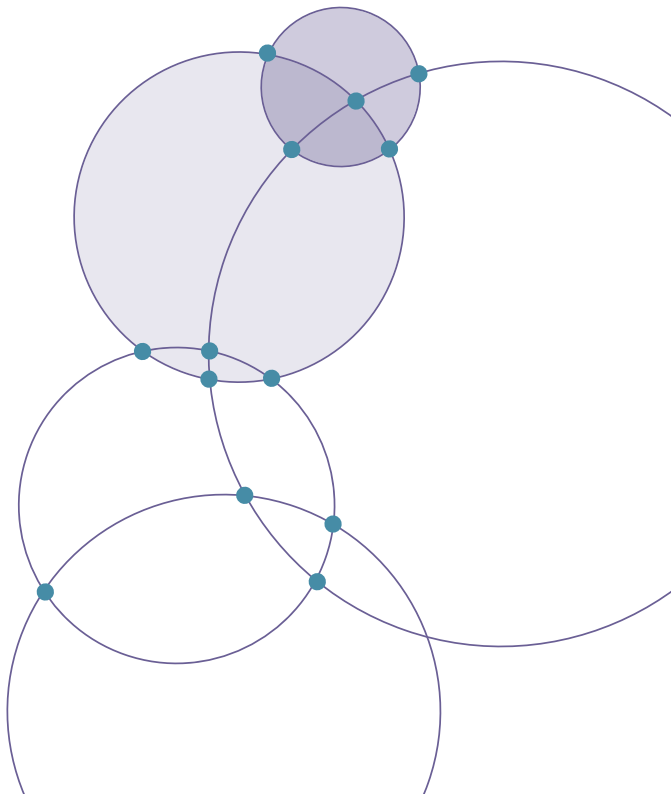


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HER2+ Breast Cancer

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.

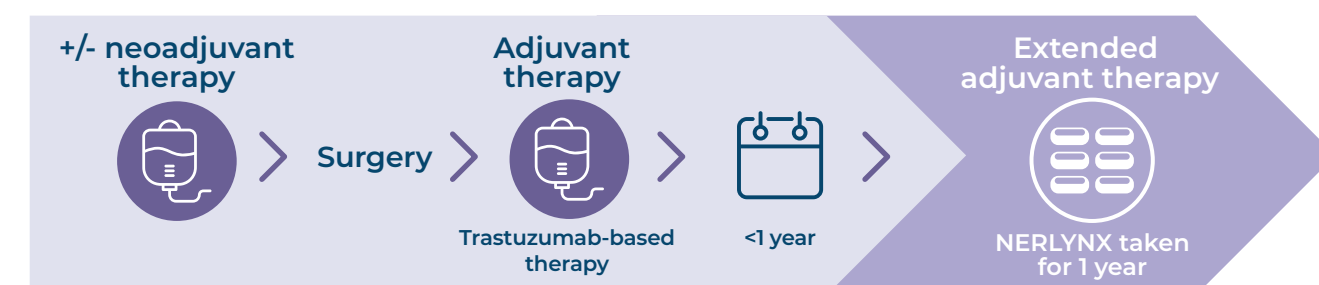


Concept of adjuvant therapy

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.

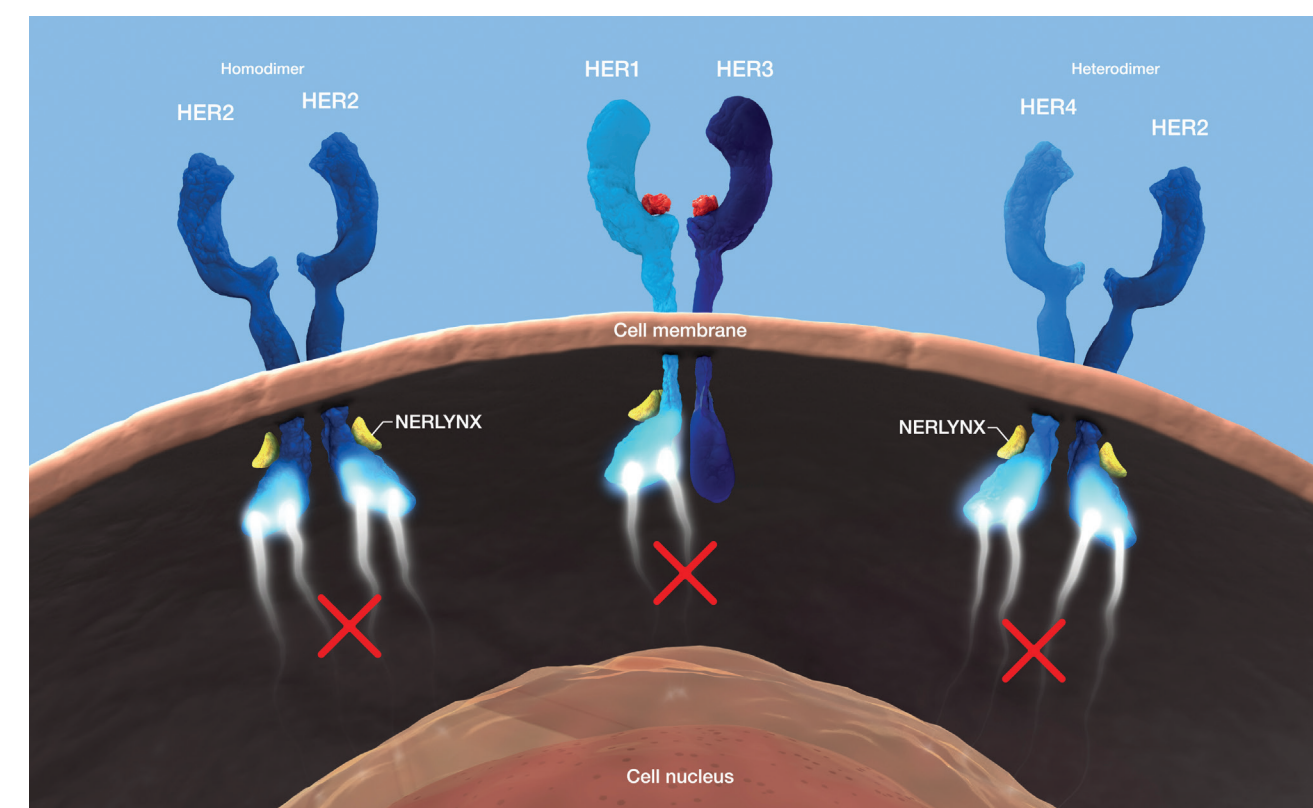
NERLYNX is indicated for the extended adjuvant treatment of adult patients with early-stage breast cancer⁵

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



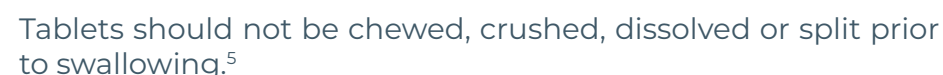
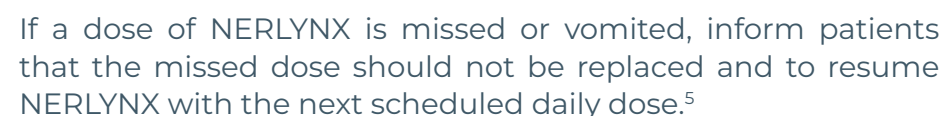
NERLYNX is a tyrosine kinase inhibitor (TKI) that penetrates the cell membrane to target the intracellular domain of the HER receptors, HER1, HER2 and HER4.^{6,7}

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



- General population

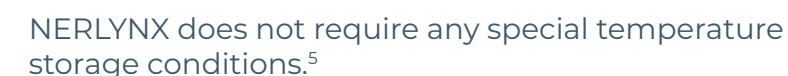
NERLYNX should be initiated within 1 year after completion of adjuvant trastuzumab-based therapy⁵



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.



- 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 tightly closed in order to protect from moisture.
- Shelf life : 3 years.¹¹

—○ LIST OF EXCIPIENTS¹¹

Tablet core

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

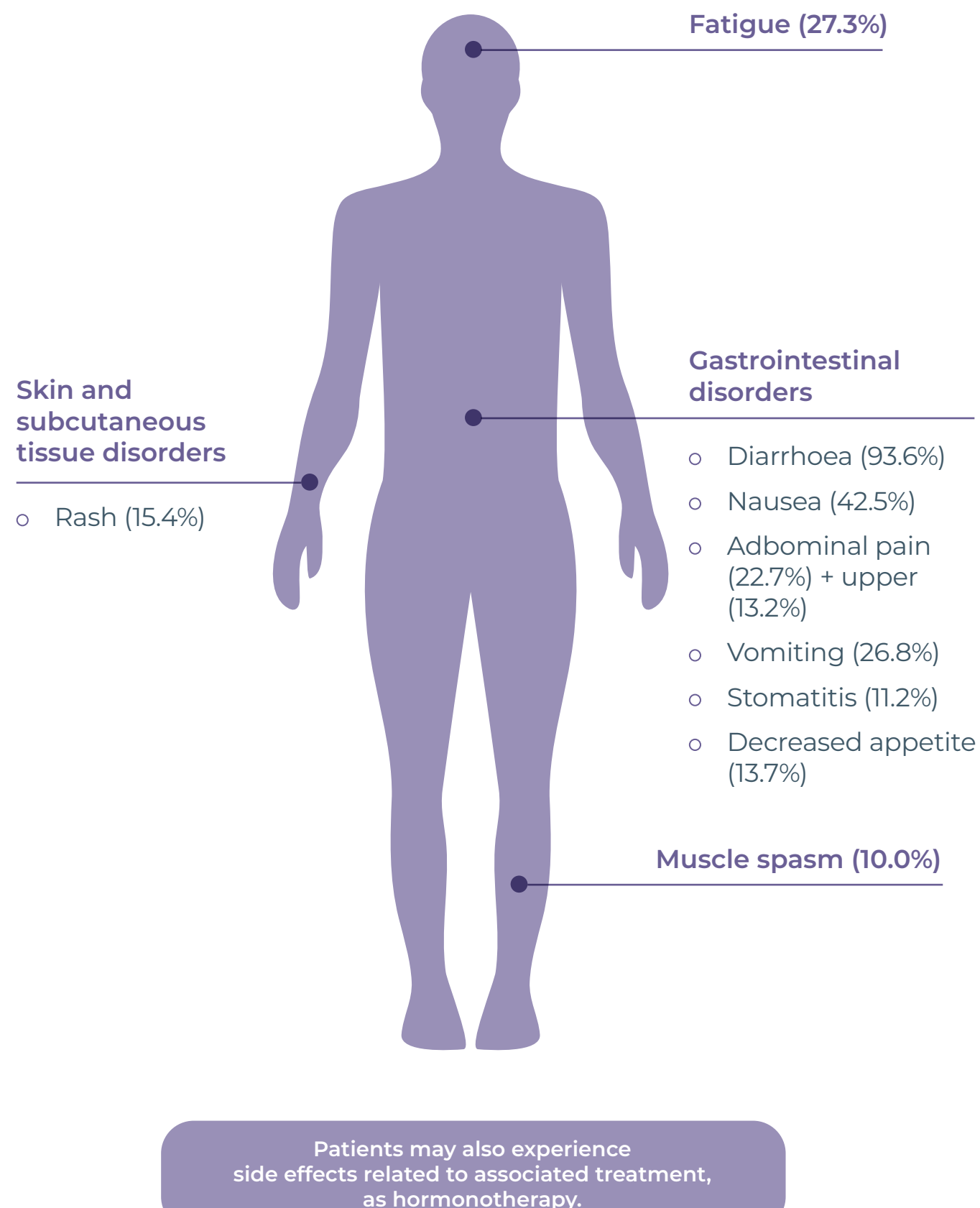
Tablet coating

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

**180 tablets
for 1 month
of treatment**

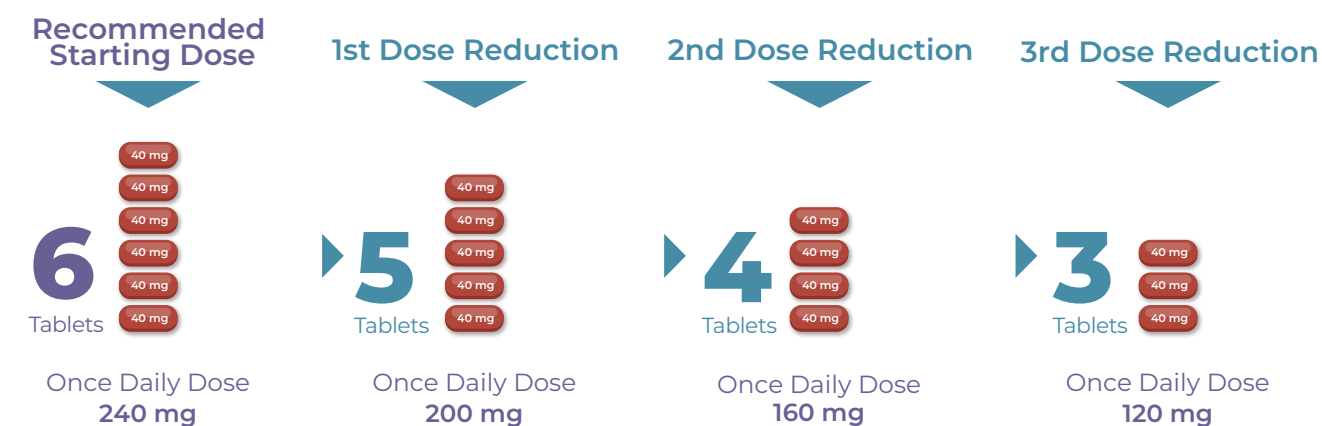
**Standard
Dosing**
240 mg
each day

- Side effects mostly reported with NERLYNX⁵



- For general adverse events

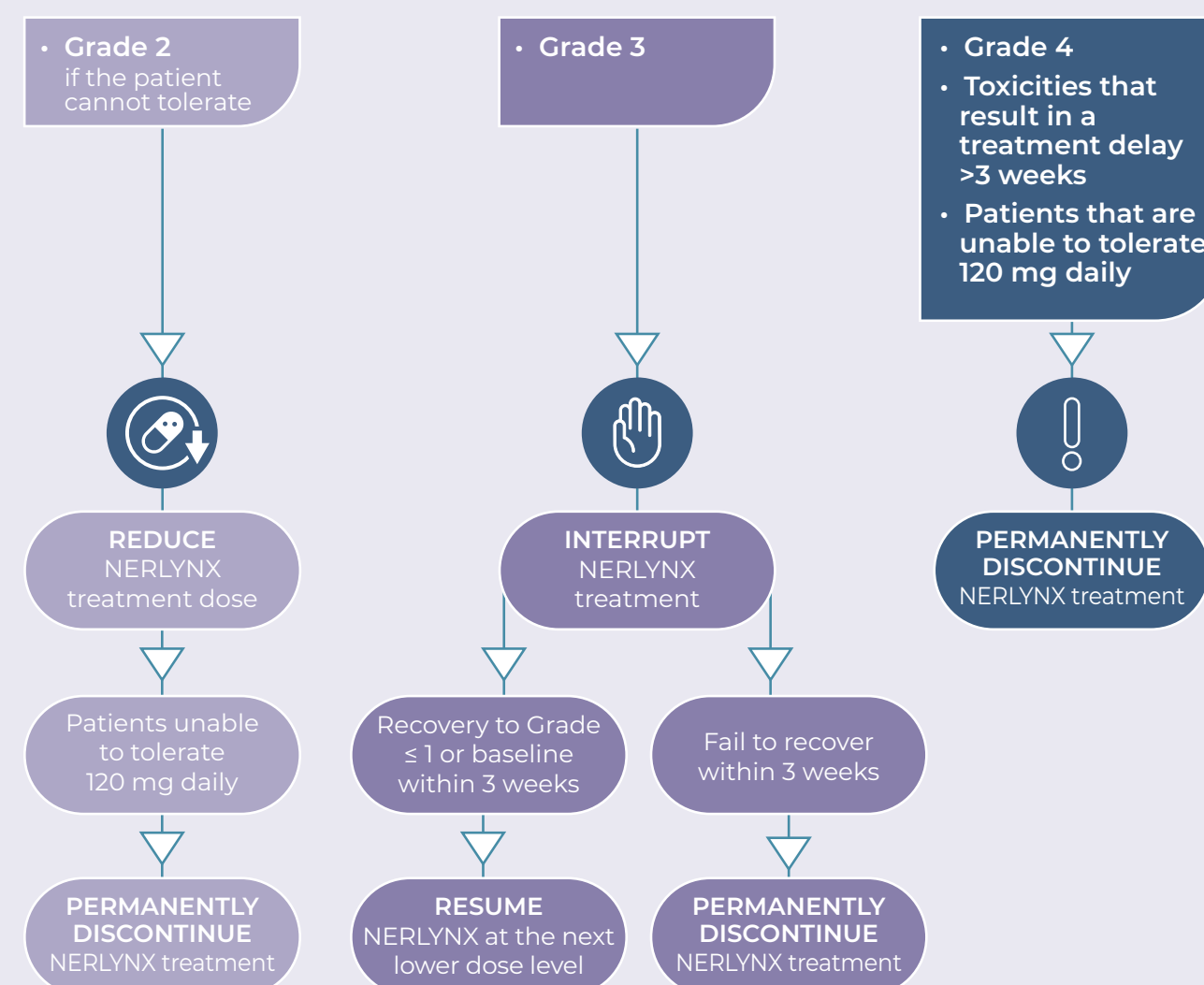
Management of some adverse reactions may require dose interruption and/or dose reduction. Adjusting daily dose can improve tolerability and adherence.⁵



- Management according to the severity of adverse reactions and based on patient individual safety and tolerability⁵

General adverse events⁵

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



○ Specific populations

Elderly⁵

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

Renal impairment⁵

- 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 m²) including patients on dialysis. Treatment is not recommended.

Hepatic impairment⁵

- 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 score¹²

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-group¹²

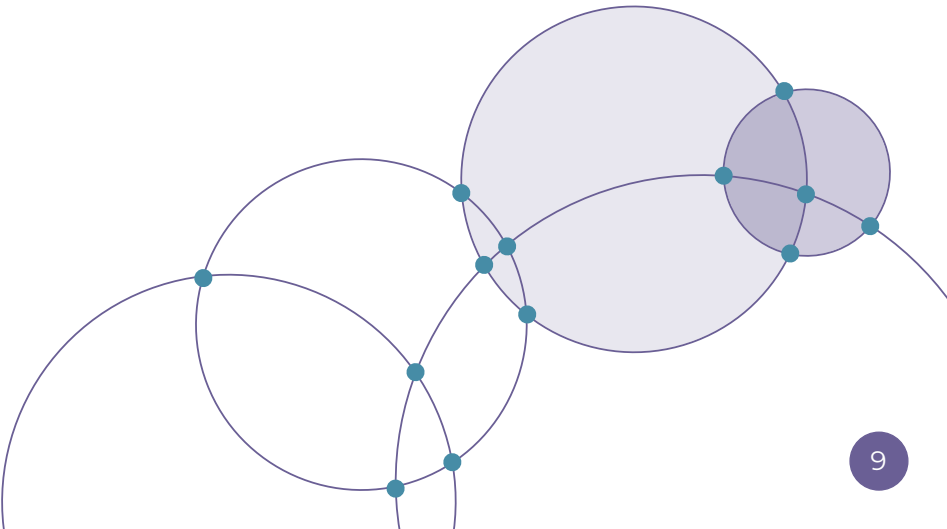
Sum of points	5-6	7-9	10-15
Class	A (mild)	B (moderate)	C (severe)

○ 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

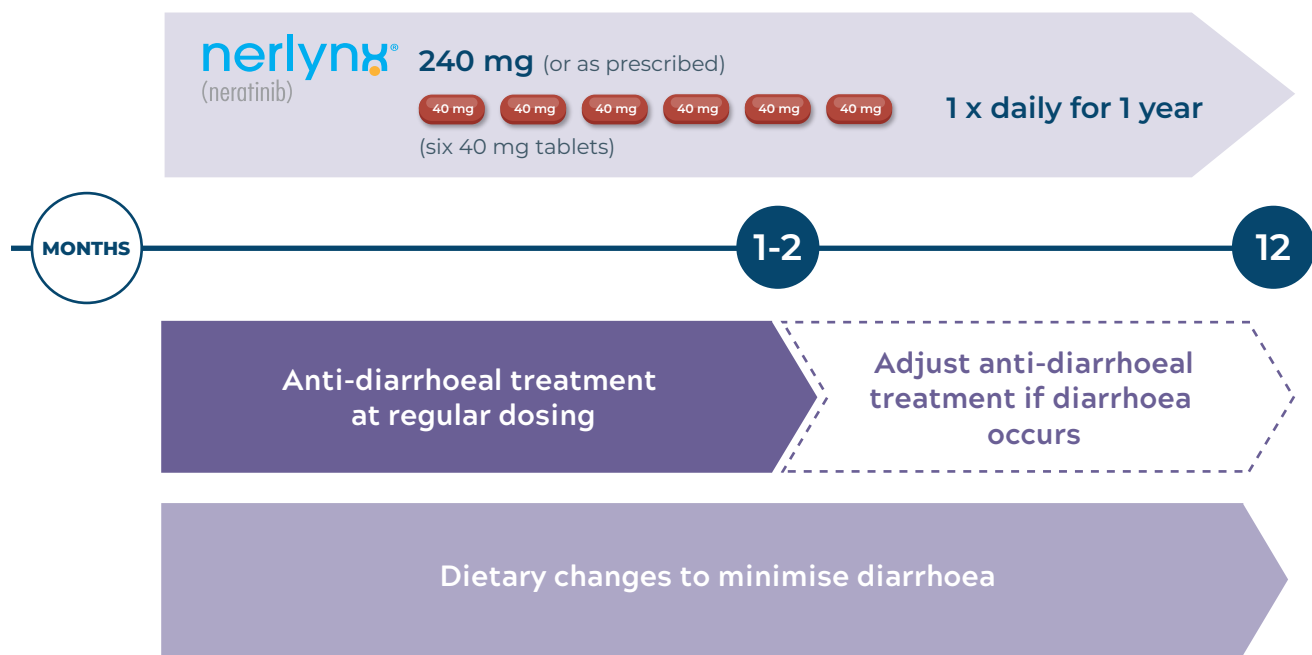
Severity of hepatotoxicity*	Action
• Grade 3 ALT (>5-20 x ULN) OR • Grade 3 bilirubin (>3-10 x ULN)	• Stop NERLYNX until recovery to Grade 0-1 • Evaluate alternative causes • Resume NERLYNX at the next lowest level if recovery to Grade 0-1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again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



○ 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



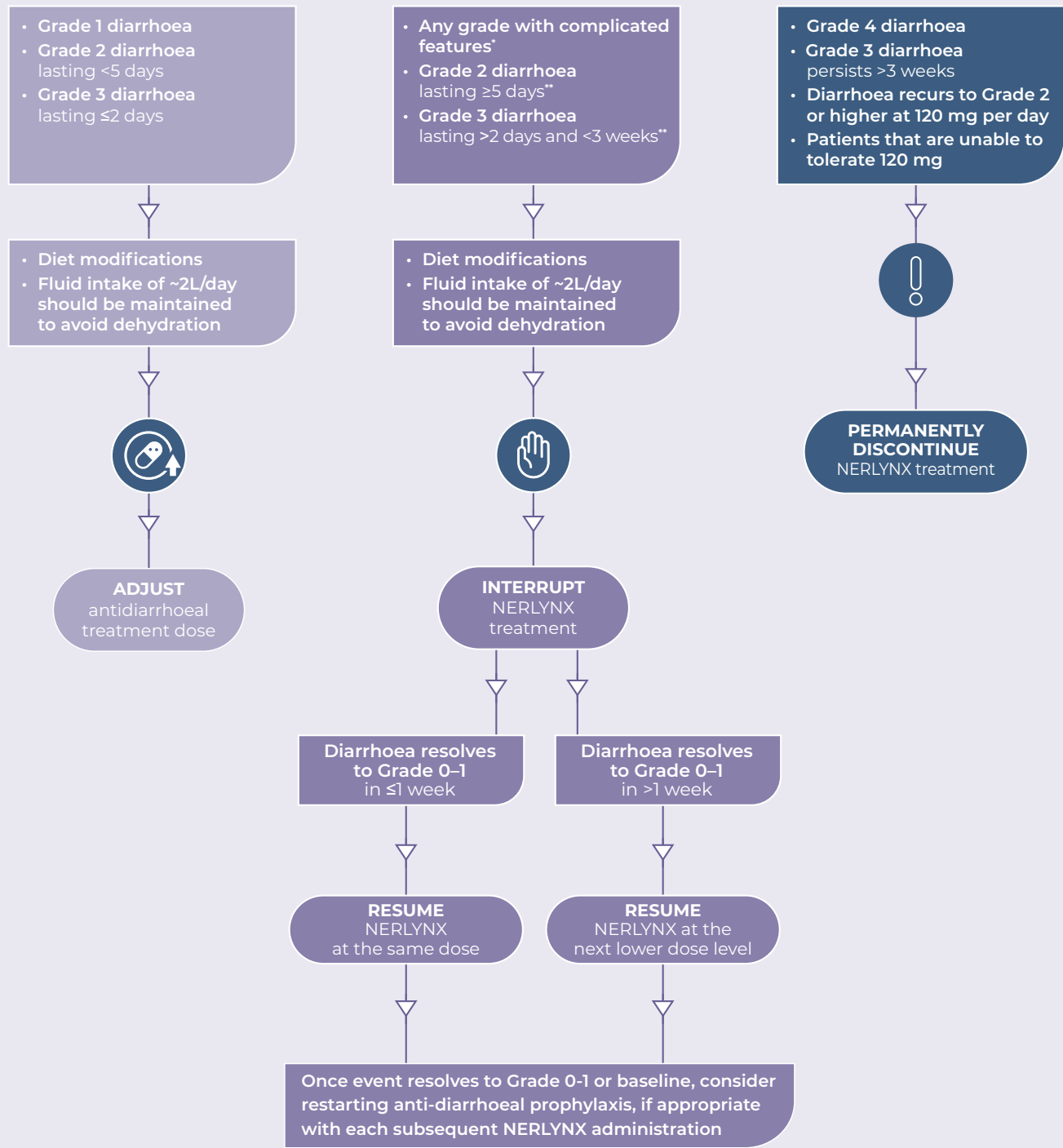
○ Management according to the severity of diarrhoea¹³

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 diarrhoea¹³

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 adjustments according to the severity of diarrhoea and based on patient individual safety and tolerability⁵



* 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

○ Contraindications⁵

- 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), macrogol, 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	<ul style="list-style-type: none">• carbamazepine, phenytoin (antiepileptics)• St John's wort (<i>Hypericum perforatum</i>) (herbal product)• rifampicin (antimycobacterial)

○ Overdose⁵

- 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-feeding⁵

- 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.

Interactions⁵

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, dexpanoprazole, 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 (<i>Hypericum perforatum</i>)
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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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 efficacy¹⁶

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 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.



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

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).



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