nerlynx®
(neratinib)

EDUCATIONAL MATERIAL
GUIDE FOR HEALTHCARE PROFESSIONALS ON
DIARRHOEA MANAGEMENT

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

This document is part of the Risk Management Plan (RMP) for NERLYNX.

In addition, Patient Educational Materials are available and should be provided systematically to the patient at initiation of NERLYNX therapy. These materials include:

- **Patient Information Leaflet**
- **Patient/Carer Treatment Guide**
- **Patient Treatment Journal**

NERLYNX is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER-2overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.[1]

For a complete information on NERLYNX, please refer to the NERLYNX Summary of Product Characteristics (SmPC).[1]

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Pierre Fabre

INTRODUCTION AND GOALS[2]

The aim of this guide is to provide healthcare professionals (HCPs) with information on the risk of severe diarrhoea and the management of diarrhoea when prescribing NERLYNX.

Patients must be informed about this risk.

The main objectives are to provide:

- Information on diarrhoea
- Information on patients at risk of diarrhoea
- Information on diarrhoea management:
  prevention, NERLYNX dose modifications, dietary changes
- Information on how to report adverse reactions

NERLYNX IN PRACTICE[1]

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

Therapeutic indication

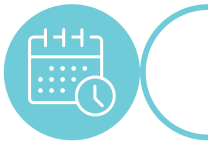
NERLYNX is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER-2overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

Recommended dose

The recommended dose of NERLYNX is 240 mg daily, to be taken orally as a single dose of six (40 (6 mg tablets, continuously for one year.

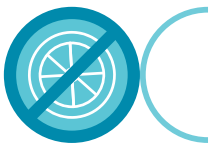
Mode of administration

Always start anti-diarrhoeal medication at initiation of NERLYNX treatment (primary anti-diarrhoeal prophylaxis).



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

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



Grapefruit or pomegranate, or grapefruit/pomegranate juice in any form should be avoided during treatment with NERLYNX.

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.

INFORMATION ON THE RISK OF DIARRHOEA[1,3,4,5,6]

The overall management of diarrhoea is based upon its grade as measured by NCI CTCAE version 4.0.

Grade 1	**Increase of up to 3 stools per day over baseline** Mild increase in ostomy output compared to baseline
Grade 2	**Increase of 6-4 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

Table 1: Severity of Diarrhoea (NCI CTCAE version 4.0)

NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events.

Of the 1,660 patients treated with NERLYNX monotherapy without loperamide prophylaxis (incl. ExteNET trial):[1]

- %94.6 experienced at least 1 episode of diarrhoea;
- %37.5 reported Grade 3 diarrhoea and %0.2 reported Grade 4 diarrhoea;
- %14.4 discontinued NERLYNX and dose reductions occurred in %24.7;
- %1.9 have been hospitalised.

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 (median time to first onset was 2 days).

In the ExteNET study, the median time to onset for Grade ≥ 3 events with NERLYNX was 8 days, and for any-grade diarrhoea was 2 days.[3]

The median duration of a single episode of any Grade diarrhoea was 2 days.[1]

The median frequency of diarrhoea of any Grade was 8 episodes per patient[6] with a median cumulative duration of 59 days; and the median cumulative duration of Grade 3 diarrhoea was 5 days.[1]

The diarrhoea may be severe and associated with dehydration.

Time course of the incidence and severity of diarrhoea: Grades 2 and 3 from the ExteNET trial[4,5]

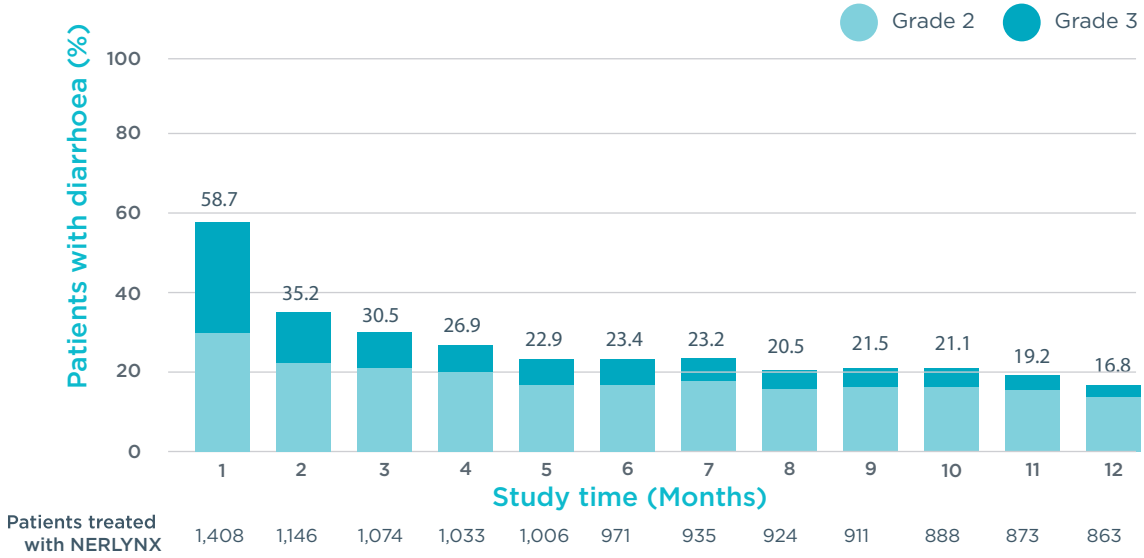


Figure adapted from Chan A. *et al.* 2016 and neratinib EPAR for ExteNET population without prophylactic anti-diarrhoeal treatment.

Of note, in ExteNET, the occurrence of diarrhoea with NERLYNX did not appear to affect clinical outcomes: patients with diarrhoea during the first 7 days of initiating NERLYNX appeared to have similar iDFS Kaplan-Meier curves over 2 years as those reporting no diarrhoea within the first 7 days.[6]

At risk of diarrhoea population:[1,2,6]

Patients at risk of diarrhoea include those with any cause of chronic or intermittent diarrhoea such as significant chronic active inflammatory bowel disease or recent acute gastrointestinal disorder with diarrhoea as a major symptom (e.g. Crohn's disease, ulcerative colitis, malabsorption, or Grade ≥ 2 diarrhoea of any aetiology prior to treatment).[1,2]

Aggravating risk factors include concomitant medications and other predisposing conditions including advanced age and renal impairment.[1,2]

Race was the only baseline factor significantly associated with the occurrence of higher-grade diarrhoea. Asian patients were significantly more likely to experience higher-grade diarrhoea versus white patients, and patients of other races were significantly less likely to experience higher-grade diarrhoea versus white patients.[6]

DIARRHOEA MANAGEMENT

Diarrhoea during NERLYNX treatment can be managed by:[1]

1. Prophylactic treatment with anti-diarrhoeal medicinal product.
2. Appropriate dose modifications of NERLYNX (according to the severity of diarrhoea).
3. Dietary changes in the setting of diarrhoea.

1. Anti-diarrhoeal prophylaxis:

Anti-diarrhoeal prophylaxis has been shown to decrease the incidence and severity of diarrhoea in patients treated with NERLYNX.[7]

Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product with the first dose of NERLYNX.[1]

Anti-diarrhoeal prophylaxis is recommended during the first one to two months of NERLYNX therapy and should be initiated with the first dose and continued after if needed.[1]

If, despite this anti-diarrhoeal prophylaxis, diarrhoea occurs, anti-diarrhoeal treatment adjustment, dose interruptions and/or dose reductions of NERLYNX may be required (see Tables 2 and 3).

2. NERLYNX dose modifications for diarrhoea:

Guidelines for adjusting doses of NERLYNX in the setting of diarrhoea are shown in the tables below.

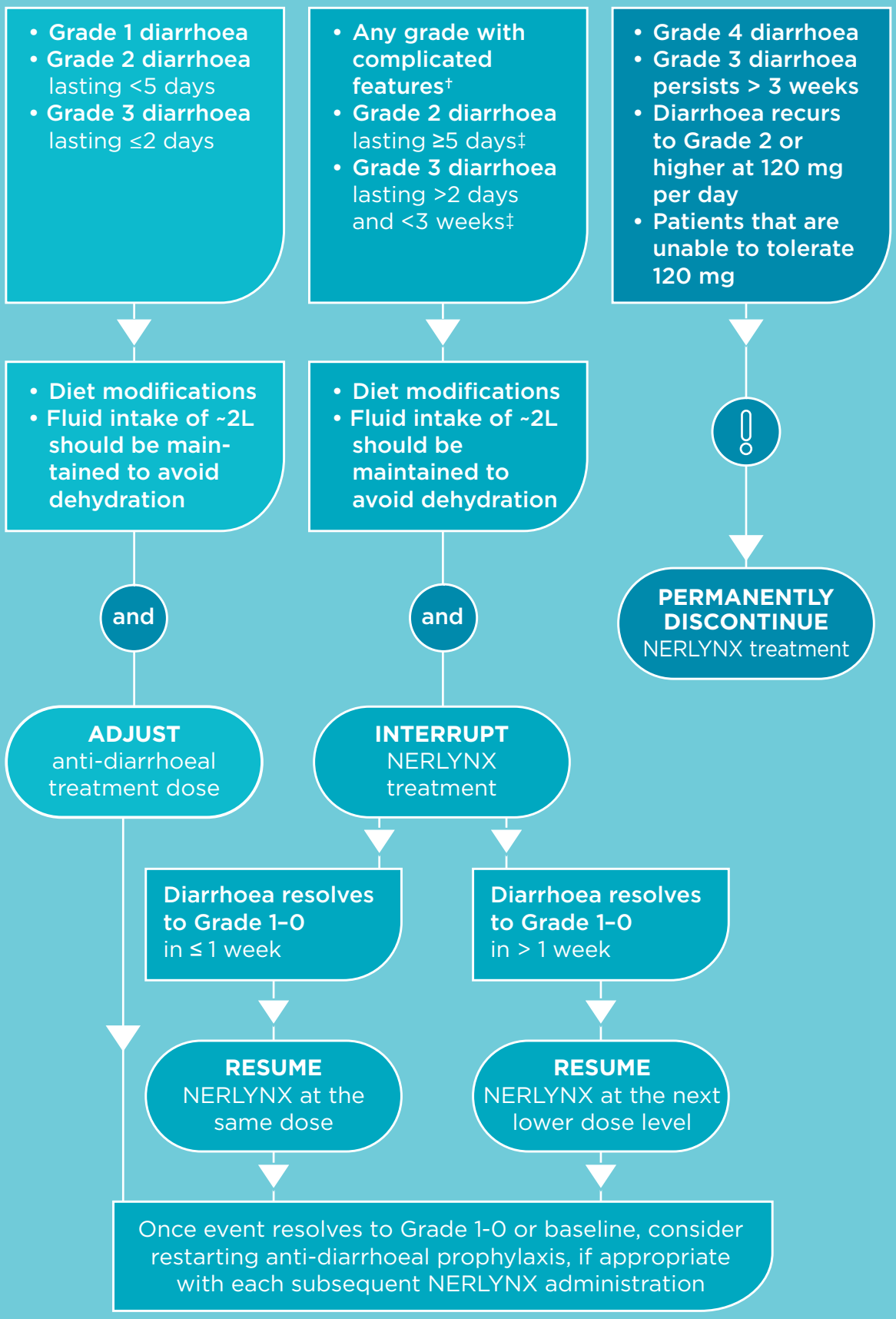
Dose level	NERLYNX dose
Recommended starting dose	240 mg daily (6 x 40 mg tablets)
First dose reduction	200 mg daily (5 x 40 mg tablets)
Second dose reduction	160 mg daily (4 x 40 mg tablets)
Third dose reduction	120 mg daily (3 x 40 mg tablets)

Table 2: NERLYNX dose modifications[1]

Other toxicities may require dose interruption and/or dose reduction (see accompanying SmPC).

OVERALL MANAGEMENT ACCORDING TO THE SEVERITY OF DIARRHOEA

Table 3: NERLYNX dose modifications according to the severity of diarrhoea[1]



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

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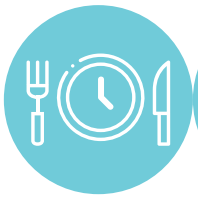
3. Dietary changes in the setting of diarrhoea:

Depending on the patients' condition and lifestyle, the following options may be considered to help to manage their diarrhoea: [8,9]

THINGS TO DO:



Eat small, frequent meals

Drink more clear liquids

Try to drink ~2L of clear fluids per day. These may 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 may include bananas, rice, applesauce, and toast

THINGS TO AVOID:

Medicines such as laxatives or stool softeners

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

FURTHER IMPORTANT INFORMATION

In addition to this guide, Educational Materials dedicated to patients are available and should be delivered to patients at initiation of NERLYNX therapy:

- Patient Information Leaflet,
- Patient Treatment Guide,
- Patient Treatment Journal.

These are intended to increase patient awareness regarding the risk of adverse effects, especially diarrhoea, and to encourage patients to contact a healthcare professional if they do experience such adverse reactions.

Patients should be instructed to fill in the Patient Treatment Journal on a daily basis, and further instructed that they should bring this Journal with them at each appointment with their HCP, in order to assist with the management of diarrhoea.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization 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
National Pharmacovigilance and Drug Safety Centre (NPC) /
Saudi Food and Drug Authority (SFDA):
o SFDA call center: 19999
o E-mail: npc.drug@sfda.gov.sa
o Website: http://ade.sfda.gov.sa/
o QR Code:

and/or to the Pharmacovigilance department of Pierre Fabre laboratories:
RAPMS@tamergroup.com
For extra copies, please contact RAPMS@tamergroup.com

References:

1. NERLYNX Summary of Product Characteristics (SmPC). May 2023.
2. NERLYNX Risk Management Plan, February 2023.
3. Mortimer J et al. Patterns of occurrence and implications of neratinib-associated diarrhea in patients with HER-2positive breast cancer: analyses from the randomized phase III ExteNET trial. Breast Cancer Res. 2019 Feb 27; 21(1):32 Electronic Supplementary Material.
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8. https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/diarrhea.
9. https://www.cancer.gov/about-cancer/treatment/side-effects/constipation/GI-complications-pdq#_29.

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