nerlynx® (neratinib)

RISK MINIMISATION GUIDE FOR HEALTHCARE PROFESSIONALS ON **DIARRHOEA MANAGEMENT**

In addition to this booklet, 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 human epidermal growth factor-2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.[1]

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

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie. Suspected adverse reactions should also be reported to Pierre Fabre Ltd: UKDrug.safety@pierre-fabre.com or 1800 812 464.

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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® (neratinib).

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, and/or 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

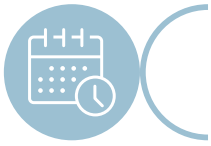
Nerlynx® is indicated for the extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

Recommended dose

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

Mode of administration

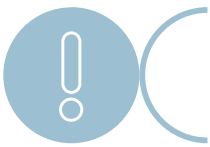
Always start anti-diarrhoeal medication at initiation of Nerlynx® treatment (primary anti-diarrhoeal prophylaxis).



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

Tablets should not be chewed, crushed, or dissolved 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, 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]

Of the 1,660 patients treated with Nerlynx® monotherapy without loperamide prophylaxis (including the 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% were 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).[1]

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

The median cumulative duration of any-grade diarrhoea was 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[3]

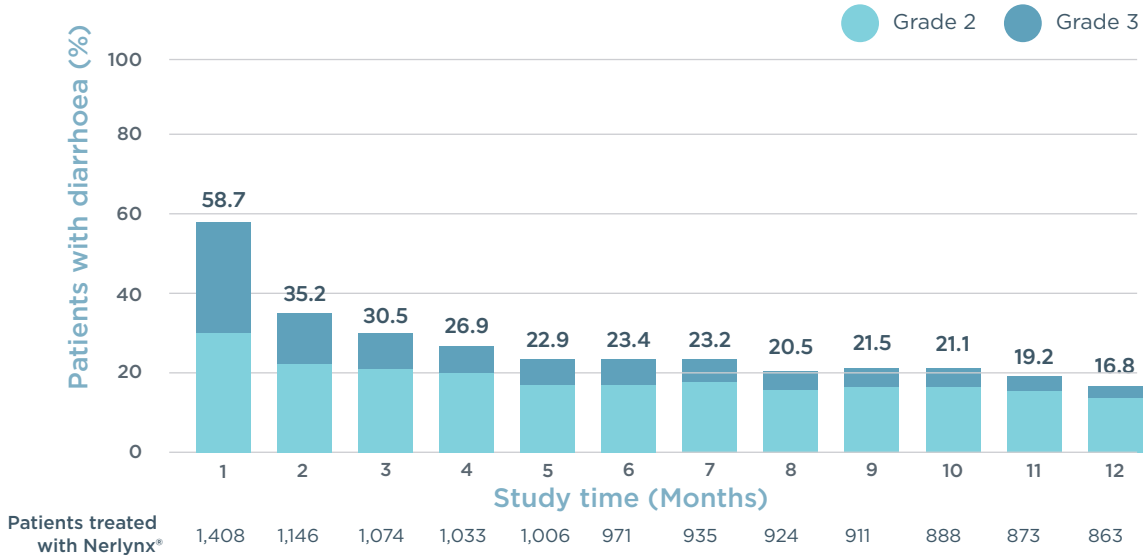


Figure adapted from neratinib EPAR for ExteNET population without prophylactic anti-diarrhoeal treatment.

INFORMATION ON THE RISK OF DIARRHOEA

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

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

Table 1: Severity of Diarrhoea

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

At risk of diarrhoea population:[1,2]

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]

DIARRHOEA MANAGEMENT

Diarrhoea during Nerlynx® treatment can be managed by:[1]

1. Prophylactic treatment with an 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:

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.

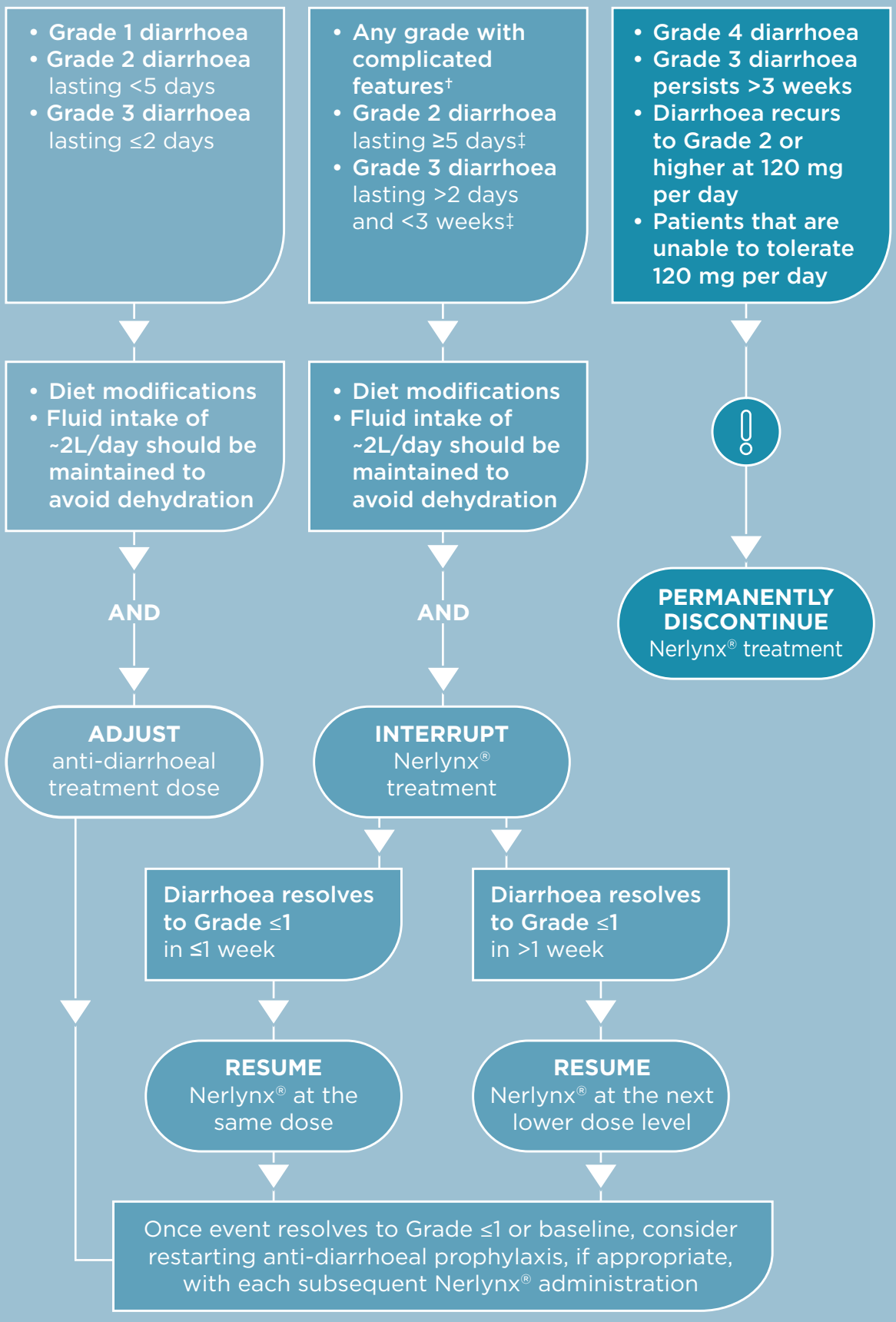
Dose level	Nerlynx® dose
Recommended starting dose	240 mg daily (6 x 40 mg tablets)
First dose reduction	200 mg daily (5 x 40 mg tablets)
Second dose reduction	160 mg daily (4 x 40 mg tablets)
Third dose reduction	120 mg daily (3 x 40 mg tablets)

Table 2: Nerlynx® dose modifications[1]

Other toxicities may require dose interruption and/or dose reduction (please refer to the Nerlynx® SmPC).

OVERALL MANAGEMENT ACCORDING TO THE SEVERITY OF DIARRHOEA

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

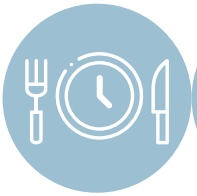


† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia.
‡ Despite being treated with optimal medical therapy.

3. Dietary changes in the setting of diarrhoea:

Patients should be instructed to adapt their diet in order to minimise diarrhoea. Consider these options to help your patients manage diarrhoea:

THINGS TO DO:



Eat small, frequent meals

Drink more clear liquids

Try to drink ~2L of clear fluids per day. These may include water, broth, weak decaffeinated tea, and clear juices.

Choose foods that are easy to digest

(low-residue diet)
These may include bananas, rice, apple sauce, and toast (white bread).

THINGS TO AVOID:

Medicines such as laxatives or stool softeners

Caffeine, alcohol, dairy, foods high in fat or fibre, 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

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: **www.hpra.ie**. Suspected adverse reactions should also be reported to Pierre Fabre Ltd: **UKDrug.safety@pierre-fabre.com** or 1800 812 464.

References:
1. Nerlynx® **(neratinib)** Summary of Product Characteristics (SmPC).
2. Nerlynx® **(neratinib)** Risk Management Plan.
3. European Medicines Agency Public Assessment Report (EPAR). Nerlynx® EMA/CHMP/525204/2018.

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