## UPDATED PRESCRIBING INFORMATION
DOSE ESCALATION IN HER2+ eBC AND mBC[1]

# nerlynx®
(neratinib) tablets

# DOSE-ESCALATION GUIDE


NERLYNX is available in a 133-tablet bottle to support dose escalation

**INDICATIONS: NERLYNX® (neratinib) tablets, for oral use,** is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

## Select IMPORTANT SAFETY INFORMATION

**Diarrhea:** Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated.

**Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated.

**Embryo-Fetal Toxicity:** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

eBC: early-stage breast cancer; mBC: metastatic breast cancer.

**Please see additional IMPORTANT SAFETY INFORMATION throughout this brochure and accompanying Full Prescribing Information.**

# Update: Dose escalation in HER2+ eBC[1]

## START NERLYNX AT A LOWER DOSE AND TITRATE UP TO THE FULL RECOMMENDED DOSE TO HELP MANAGE DIARRHEA[1]

### NERLYNX dose escalation

| DAYS 1-7 | DAYS 8-14 | DAY 15+ |
|---|---|---|
| 3 Tablets 120 mg once daily | 4 Tablets 160 mg once daily | 6 Tablets 240 mg once daily |

+ LOPERAMIDE AS NEEDED (not to exceed 16 mg/day)*

CONTROL was a phase 2, open-label, nonrandomized, multicenter, multinational study to evaluate the effect of dose escalation or antidiarrheal prophylaxis on diarrhea associated with NERLYNX. NERLYNX dose-escalation arm in CONTROL: n=60.[2]

ExteNET was a pivotal phase 3, global, multicenter, randomized, double-blind, placebo-controlled study. NERLYNX arm in ExteNET: n=1408. Antidiarrheal prophylaxis was not protocol mandated.[2]

**A CROSS-STUDY, DESCRIPTIVE ANALYSIS OF THE DOSE-ESCALATION ARM IN CONTROL (n=60) AND NERLYNX ARM IN ExteNET (n=1408)[1]**

**>65% reduction in rate of grade 3 diarrhea†**

- Rate of grade 3 diarrhea: 13% with NERLYNX dose escalation vs 40% with NERLYNX in ExteNET

**50% reduction in median days of grade ≥3 diarrhea†**

- Median cumulative days of grade ≥3 diarrhea: 2.5 days with NERLYNX dose escalation vs 5 days with NERLYNX in ExteNET

**>80% reduction in rate of discontinuations due to diarrhea†**

- Treatment discontinuations due to diarrhea: 3.3% with NERLYNX dose escalation vs 17% with NERLYNX in ExteNET

- Recommended dose in HER2+ eBC: 240 mg orally once daily, with food, taken continuously until disease recurrence for up to one year[1]
- Loperamide-prophylaxis arm of CONTROL: 32% grade 3 diarrhea (n=109), 3-day median cumulative duration of grade ≥3 diarrhea (n=137), and 18% discontinuation rate due to diarrhea (n=109)[1,2]

* If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated.[1]
† Dose-escalation arm (n=60): NERLYNX 120 mg/day on days 1-7, 160 mg/day on days 8-14, 240 mg/day from days 15-364.[1]

## Select IMPORTANT SAFETY INFORMATION

**Diarrhea:** Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥2 diarrhea that occurs after maximal dose reduction.

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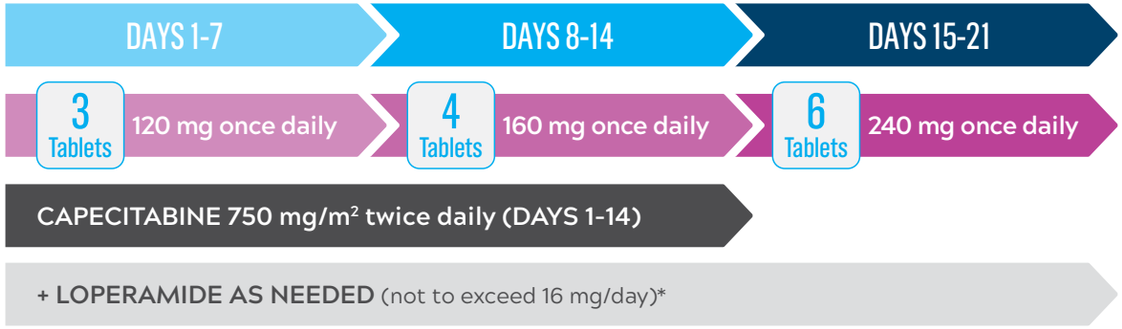
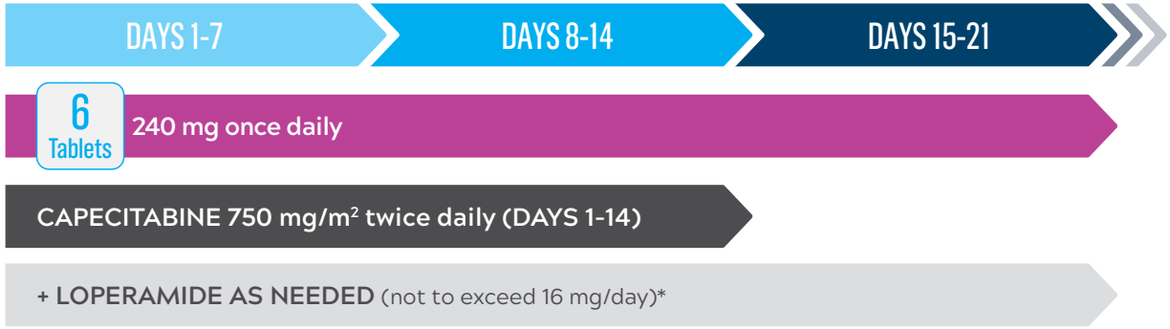
# Update: Dose escalation in HER2+ mBC[1]

## NERLYNX + CAPECITABINE IS ADMINISTERED IN A 21-DAY DOSING CYCLE

### Cycle 1—NERLYNX dose escalation




### Cycle 2 and beyond—full recommended NERLYNX dose




* If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated.[1]
† Refer to the capecitabine Prescribing Information when NERLYNX is used in combination with capecitabine.

- Recommended dose in HER2+ mBC: 240 mg orally once daily, with food, taken continuously until disease progression or unacceptable toxicities[1]
- Instruct patients to take capecitabine with water within 30 minutes after a meal on days 1 to 14 of each 21-day cycle[3,†]

### IMPORTANT DOSING INFORMATION

- When not using dose escalation, initiate loperamide with the first dose of NERLYNX and continue until day 56. After day 56, use loperamide as needed to maintain 1-2 bowel movements per day
- Dose interruptions and/or dose reductions are recommended based on individual safety and tolerability
- Hepatic impairment: Reduce starting dose to 80 mg in patients with severe hepatic impairment
- Discontinue NERLYNX for patients with adverse reactions that fail to recover to grade 0-1 or baseline, with toxicities that result in a treatment delay >3 weeks, or if unable to tolerate 120 mg daily
- Instruct patients:
  - To take NERLYNX with food at approximately the same time every day
  - To swallow NERLYNX whole (tablets should not be chewed, crushed, or split prior to swallowing)
  - To not replace a missed dose and resume NERLYNX with the next scheduled daily dose

## Select IMPORTANT SAFETY INFORMATION

**Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.

**Please see additional IMPORTANT SAFETY INFORMATION throughout this brochure and accompanying Full Prescribing Information.**

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**A voucher program for up to 3 months' FREE supply of antidiarrheals is available to all patients. Vouchers can be obtained from your sales representative or one of the Puma network specialty pharmacies.**

## Learn more at nerlynxHCP.com

The voucher can be used at any retail pharmacy. Qualifying guidelines and additional utilization instructions are provided on the voucher. This program may be changed or discontinued at any time. Limitations apply.

## IMPORTANT SAFETY INFORMATION

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS:**

- **Diarrhea:** Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥2 diarrhea that occurs after maximal dose reduction.
- **Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.
- **Embryo-Fetal Toxicity:** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

**ADVERSE REACTIONS:** The most common adverse reactions (reported in ≥5% of patients) were:

- NERLYNX as a single agent: diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increased, nail disorder, dry skin, abdominal distention, epistaxis, weight decreased, and urinary tract infection.
- NERLYNX in combination with capecitabine: diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms.

**To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**DRUG INTERACTIONS:**

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. Separate NERLYNX by at least 2 hours before or 10 hours after $H_2$-receptor antagonists. Or separate NERLYNX by at least 3 hours after antacids.
- Strong CYP3A4 inhibitors: Avoid concomitant use.
- P-gp and moderate CYP3A4 dual inhibitors: Avoid concomitant use.
- Strong or moderate CYP3A4 inducers: Avoid concomitant use.
- Certain P-gp substrates: Monitor for adverse reactions of P-gp substrates for which minimal concentration change may lead to serious adverse reactions when used concomitantly with NERLYNX.

**USE IN SPECIFIC POPULATIONS:**

- **Lactation:** Advise women not to breastfeed.

**Please see accompanying Full Prescribing Information.**

**References:** 1. NERLYNX [package insert]. Los Angeles, CA: Puma Biotechnology, Inc. 2. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230. doi:10.1016/j.annonc.2020.05.012 3. Puma Biotechnology, Inc. Data on file.

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