Neratinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Extended adjuvant treatment of adults with early-stage hormone receptor-positive, HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.	C50	00720a	CDS 01/03/2022

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Neratinib is taken orally, once daily continuously for one year, unless disease progression or unacceptable toxicities. Patients should initiate treatment within 1 year after completion of trastuzumab therapy.

Drug	Dose	Route	Cycle
Neratinib	240mg once daily	PO[a, b]	Continuous
[a]Neratinib should be taken with food, preferably in the morning.			
[b]Missed doses should not be replaced and treatment should resume with the next scheduled daily dose			

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Left ventricular ejection fraction (LVEF) within normal range
- Adequate organ function

CAUTION:

- Left ventricular ejection fraction (LVEF) of 45% or less
- Any condition that increases the risk of serious dehydration or biochemical disturbance associated with severe diarrhoea e.g. elderly, frail or chronic gastrointestinal disorder with associated diarrhoea.

EXCLUSIONS:

- Hypersensitivity to neratinib or any of the excipients
- History of heart disease
- Corrected QT (QTc) interval >0.45 seconds
- History of gastrointestinal disease with diarrhoea as the major symptom
- Severe hepatic impairment (Child-Pugh C)

- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, and hepatic profile
- Cardiac function including LVEF if clinically indicated

Regular tests:

- FBC and LFTs monthly for the first 3 months

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose modification of neratinib is recommended based on individual safety and tolerability.
- Neratinib should be discontinued for patients who
    - Fail to recover to grade 0-1 from treatment-related toxicity
    - For toxicities that result in a treatment delay >3 weeks, or
    - For patients that are unable to tolerate 120mg daily
- Management of some adverse reactions may require dose interruptions and/or dose reduction. Please refer to Table 1 for dose levels. Please refer to Table 2 for neratinib dose modifications for adverse reactions. Please refer Tables 3 to 5 for the management of neratinib toxicities.

Table 1: Neratinib dose modifications for adverse reactions

Dose level	Neratinib dose
Recommended starting dose	240mg daily
First dose reduction	200mg daily
Second dose reduction	160mg daily
Third dose reduction	120mg daily

Haematological:

Table 2: Dose modification of neratinib in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
ANC≤ 0.9	and	≤99	Delay by 1 week

Renal and Hepatic Impairment:

Table 3: Dose modification of neratinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment	
No dose adjustment is necessary for mild to moderate renal impairment. Neratinib has not been studied in patients with severe renal impairment including patients on dialysis. Treatment of patients with severe renal impairment or on dialysis is not recommended	**Severity of hepatotoxicity***	**Action**
	Grade 3 ALT (>5-20 x ULN) Or Grade 3 bilirubin (>3-10 x ULN)	• Stop neratinib until recovery to Grade 0-1 • Evaluate alternatives causes • Resume neratinib at the next lower dose 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 neratinib. • If grade 3 hepatotoxicity persists longer than 3 weeks, discontinue neratinib **permanently.**
	Grade 4 ALT (>20 x ULN) Or Grade 4 bilirubin (>10 xULN)	• Permanently discontinued neratinib • Evaluate alternative causes
	No dose adjustment is required in patients with Child-Pugh A or B (mild to moderate) hepatic impairment.	

ULN=Upper Limit Normal; ALT= Alanine Aminotransferase
* Per CTCAE v4.0

Management of adverse events:

Table 4: Neratinib dose modifications and management- general toxicities

Severity of toxicity*	Recommended dose modification
Grade 3	Stop neratinib until recovery to Grade 0-1 or baseline within 3 weeks of stopping treatment. Then resume neratinib at the next lower dose level. If grade 3 toxicity does not recover within 3 weeks, discontinue neratinib permanently.
Grade 4	Discontinue neratinib permanently

*Per CTCAE v4.0

Table 5: Neratinib dose modifications for diarrhoea

Severity of toxicity*	Recommended dose modification
• Grade 1 diarrhoea (increase of <4 stools per day over baseline) • Grade 2 diarrhoea (increase of 4-6 stools per day over baseline) lasting <5 days • Grade 3 diarrhoea (increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living) ≤2 days	• Adjust anti-diarrhoeal treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration Once event resolves to Grade 0-1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration.
• Any grade with complications features† • Grade 2 diarrhoea lasting 5 days or longer‡ • Grade 3 diarrhoea lasting between 2 days and 3 weeks ‡	• Interrupt neratinib treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • If diarrhoea resolves to Grade 0-1 in one week or less, then resume neratinib treatment at the same dose. • If diarrhoea resolves to Grade 0-1 in longer than one week, then resume neratinib treatment at reduced dose. • Once event resolves to Grade 0-1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration. • If grade 3 diarrhoea persists longer than 3weeks, discontinue neratinib permanently.
• Grade 4 diarrhoea (life-threatening consequences; urgent intervention indicated)	• Permanently discontinued neratinib treatment.
• Dairrhoea recurs to Grade 2 or higher at 120mg per day	• Permanently discontinued neratinib treatment

* Per CTCAE v4.0

† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia

‡ Despite being treated with optimal medical therapy

Concomitant treatment with CYP3A4 and P-gp inhibitors:

- Strong and moderate inhibitors of CYP3A4 and P-gp may lead to increased toxicity. Concomitant use of strong and moderate CYP3A and P-gp inhibitors during treatment with neratinib should be avoided.
    - If co-administration with a strong inhibitor of CYP3A and P-gp is unavoidable, reduce the neratinib dose to 40mg once daily.
    - If co-administration with a moderate inhibitor of CYP3A and P-gp is unavoidable, reduce the neratinib dose to 40mg once daily. If well tolerated, increase to 80mg for at least 1 week, then to 120mg for at least 1 week, and to 160mg as a maximal daily dose. Patients should be monitored carefully, especially GI effects including diarrhoea and hepatotoxicity.
    - After discontinuation of a strong or moderate CYP3A4/P-gp inhibitor, resume previous dose of neratinib 240mg.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal prophylaxis is recommended during the first two months of treatment and should be initiated with the first dose. Anti-diarrhoeals (e.g. loperamide) should be taken as directed in the table below, titrating to 1-2 bowel movements per day.

Time on treatment	Loperamide dose	Frequency
Weeks 1-2	4mg	Three times a day
Weeks 3-8	4mg	Twice a day
Weeks 9-52	4mg	As required

Additional anti-diarrhoeal medication may be required if diarrhoea is refractory. Dose interruption and reductions may also be required.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Diarrhoea:** diarrhoea has been reported during treatment with neratinib. Diarrhoea may be severe and associated with dehydration. Diarrhoea generally occurs early during the first or second week of treatment with neratinib and may be recurrent. Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product with the first dose of neratinib, and maintain regular dosing of the anti-diarrhoeal medicinal product during the first 1-2 months of neratinib treatment, titrating to 1-2 bowel movements per day. Elderly patients are at a higher risk of renal insufficiency and dehydration which may be a complication of diarrhoea and these patients should be carefully monitored.
- **Renal impairment**: patients with renal impairment are at a higher risk of complications of dehydration if they develop diarrhoea, and these patients should be carefully monitored.
- **Liver function:** hepatotoxicity has been reported in patients treated with neratinib. Liver function tests should be monitored. Patients who experience ≥ Grade 3 diarrhoea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests.
- **Left ventricular function**: Left ventricular dysfunction has been associated with HER2 inhibition. Patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.
- **Skin and subcutaneous tissue disorders**: neratinib is associated with skin and subcutaneous tissue disorders. Patients with symptomatic skin and subcutaneous tissue disorders should be carefully monitored

- **Pregnancy:** neratinib may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking neratinib and for up to 1 month after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking neratinib and for 1 month after stopping treatment.

DRUG INTERACTIONS:

- Neratinib is primarily metabolized by CYP3A4 and is a P-gp substrate. Concomitant treatment with strong or moderate CYP3A4 and P-gp inhibitors is not recommended due to risk of increased exposure to neratinib. If the inhibitor cannot be avoided, neratinib dose adjustment should be applied, see dose modification for further details. Grapefruit or pomegranate juice should be avoided during treatment with neratinib.
- Concomitant treatment with moderate CYP3A4 and P-gp inducers is not recommended as it may lead to a loss of neratinib efficacy.
- Patients who are treated concomitantly with therapeutic agents with a narrow therapeutic window whose absorption involves P-gp transporters in the gastrointestinal tract should be carefully monitored
- Proton pump inhibitors, H2-receptor antagonists and antacids: treatments that increase gastrointestinal pH may lower the absorption of neratinib, thus decreasing systemic exposure. Co-administration with proton pump inhibitors (PPIs) is not recommended. In case of H2-receptor antagonists or antacids, modalities of administration should be adapted
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Chan A et al Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExeNET): a multicentre, randomised, double blind, placebo-controlled, phase 3 trial. Lancet Oncol.2016 Mar; 17(3):367-377.
2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
3. Nerlynx® (neratinib) Summary of Product characteristics accessed January 2022 available at https://www.ema.europa.eu/en/documents/product-information/nerlynx-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	09/02/2022		Prof Seamus O'Reilly

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