Indication	For the treatment of hormone receptor positive and HER2 overexpressed early breast cancer after completing adjuvant trastuzumab monotherapy, within the last 12 months. Patients must not have received any other adjuvant HER2 treatment other than trastuzumab. If patients have received neo-adjuvant treatment, residual invasive disease in the axilla or breast must have remained after completion of treatment.
Treatment Intent	Adjuvant (extended)
Frequency and number of cycles	Repeat every 28 days continuously for a maximum duration of 12 months. A formal medical review as to whether treatment should continue and at what dose must occur by at least the start of the second month of treatment.
Monitoring Parameters pre-treatment	• Monitor FBC and U&Es at each cycle. • LFTs should be monitored prior to treatment, after 1 week, then before each cycle or as clinically indicated. Patients who experience >/= Grade 3 diarrhoea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, should be evaluated for changes in liver function tests and prothrombin time. • Left ventricular ejection fraction (LVEF) must be >/=50% prior to commencing treatment. • In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated throughout treatment. • **Hepatic impairment:** No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. Treatment of patients with Child Pugh C hepatic impairment is contraindicated. • **Renal Impairment:** No dose adjustment is necessary in patients with mild to moderate renal impairment (CrCl >/=30 mL/min). Neratinib has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) including patients on dialysis. Treatment of patients with severe renal impairment or on dialysis is not recommended. • **Diarrhoea:** Severe diarrhoea and associated dehydration during treatment with neratinib has been reported. Patients must commence prophylactic anti-diarrhoeal medication prior to treatment and continue regularly throughout the first 1-2 months. Dosing should be titrated to achieve 1-2 bowel movements per day (see table 1). If despite prophylactic therapy and dietary management diarrhoea persists, increase loperamide to a maximum of 16mg per day, or consider the use of budesonide (9mg PO OD for 3-5 days) or octreotide (starting dose 100mcg SC/IV TDS). See also 'dose modification for adverse reactions'. • **Dose modification for adverse reactions:** ○ For grade 3 toxicities (for diarrhoea and hepatotoxicity see below), stop treatment until recovery to Grade </= 1 or baseline (which should occur within 3 weeks of stopping treatment). Then resume at the next lower dose level. Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent Grade 2 adverse reactions, etc.). For patients receiving 240mg neratinib once daily, the first dose reduction should be 200mg once daily. The 2nd dose reduction is to 160mg once a day, and the 3rd dose reduction to 120mg once a day. Treatment should be permanently discontinued for patients who: - Fail to recover to Grade 0 to 1 from treatment-related toxicity, - For toxicities that result in a treatment delay > 3 weeks,

- For patients that are unable to tolerate 120 mg daily, or
- For any Grade 4 toxicity.

- Diarrhoea:
  For any Grade 1, Grade 2 (lasting <5 days) or Grade 3 (lasting </=2 days) adjust anti-diarrhoeal medication, advise patient on appropriate diet modification and ensure a fluid intake of 2 litres is maintained.
  Once the reaction has resolved to </= Grade 1 or baseline consider restarting prophylactic anti-diarrhoeal treatment with each subsequent cycle of neratinib.
  For any Grade diarrhoea with complications (dehydration, fever, hypotension, renal failure or grade 3 or 4 neutropenia), for Grade 2 (lasting >/=5 days) or Grade 3 (lasting between 2 days – 3 weeks) withhold treatment, advise patient on appropriate diet modification and ensure a fluid intake of 2 litres is maintained.
  If diarrhoea resolves to grade 0-1 in within one week resume treatment at the same dose. If resolves in longer than 1 week resume treatment with dose reduction. Consider restarting prophylactic anti-diarrhoeal treatment with each subsequent cycle of neratinib.
  Treatment should be **permanently discontinued** if Grade 3 diarrhoea persists for longer than 3 weeks, for any Grade 4 diarrhoea or if diarrhoea reoccurs to Grade 2 or higher on 120mg per day of neratinib.
  NB the following resources are available from the SPC online at https://www.medicines.org.uk/emc/ "*risk minimisation guide for healthcare profeessionals on diarrhoea management"* and *"patient/carer treatment guide How to manage diarrhoea with nerlynx®"*
- Hepatotoxicity:
  Grade 3 ALT (>5-20 x ULN) or Grade 3 bilirubin (>3-10 x ULN), withhold neratinib until recovery to </= Grade 1, investigate alternative causes other than neratinib exposure and resume treatment at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue neratinib.
  Grade 4 ALT (>20 x ULN) or Grade 4 bilirubin (>10 x ULN) permanently stop neratinib and investigate alternative causes other than neratinib exposure.

- **Drug Interactions (for comprehensive list refer to BNF/SPC):**
- Concomitant use of neratinib with strong inducers of the CYP3A4/P-gp isoform of cytochrome P450 (e.g. phenytoin, carbamazepine, rifampicin, or herbal preparations containing St John's Wort/Hypericum perforatum) is contraindicated. Concurrent use with moderate CYP3A4/P-gp inducers (bosentan, efavirenz, etravirine, phenobarbital, dexamethasone, primidone) is not recommended.
- Concomitant treatment with strong or moderate CYP3A4 and P-gp inhibitors is not recommended. If the use of a strong CYP3A4/P-gp inhibitor (nelfinavir, ritonavir, ketoconazole, itraconazole, clarithromycin, and voriconazole) cannot be avoided, reduce neratinib dose to 40 mg once daily.
  If the use of a moderate CYP3A4/P-gp inhibitor (erythromycin, fluconazole, diltiazem and verapamil) cannot be avoided dose reduce to 40mg once daily, if well tolerated increase dose by 40mg weekly to a maximum dose of 160mg. After discontinuation of a strong or moderate CYP3A4/Pgp inhibitor, review dose and resume previous dose where appropriate.
- Grapefruit or pomegranate juice should be avoided.
- Co-administration with proton pump inhibitors (PPIs) is not recommended. If H2 antagonists are used, neratinib should be taken at least 2 hours before, or 10 hours after the H2-receptor antagonists.
- A 3-hour gap should be left between antacids and neratinib doses.

	○ Patients who are treated concomitantly with therapeutic agents whose metabolism involves P-gp substrates (e.g. digoxin, phenytoin, statins) in the gastrointestinal tract should be monitored carefully. • **Missed dose:** If a dose is missed treatment should resume with the next scheduled daily dose. Treatment breaks of up to 3 weeks are permitted, but solely to allow toxicities to settle. • Patients should be advised that neratinib may affect their ability to drive or operate machinery. • Patients must carry the (NERLYNX®) patient alert card. For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	CDF list v1.169 SPC accessed online 21/09/20 https://www.medicines.org.uk/emc/rmm/1612/Document https://www.medicines.org.uk/emc/rmm/1613/Document KMCC SACT induced diarrhoea guidelines: http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1
Anti-diarrhoeal prophylaxis:

Duration on treatment	Dose of loperamide	Administration
Week 1-2 (days 1-14)	4mg	Three times a day
Week 3-8 (days 15-56)	4mg	Twice a day
Week 9-52 (days 57-365)	4mg	As needed (not to exceed 16mg per day)

Repeat every 28 days:

TTO	Drug	Dose	Route	Directions
Day 1	Loperamide	2-4mg	PO	Take as directed to achieve 1-2 bowel movements per day (see table 1). Take TWO capsules (4mg) after first loose stool, then ONE every 2 hrs for at least 12 hrs or until 12 hrs after last loose stool (for max. of 48hrs) Maximum 16mg a day.
	NERATINIB	**240mg**	PO	OM. Swallowed whole with food. Do not crush, dissolve or chew. Available as 40mg tablets. Dispense 30 days' supply.
	Metoclopramide	10mg	PO	Up to TDS PRN Do not take for more than 5 days continuously.