Summary of risk management plan for Nerlynx (neratinib)

This is a summary of the risk management plan (RMP) for Nerlynx. The RMP details important risks of Nerlynx, how these risks can be minimised, and how more information will be obtained about Nerlynx's risks.

Nerlynx's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to HCPs and patients on how Nerlynx should be used.

This summary of the RMP for Nerlynx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Nerlynx's RMP.

I. The medicine and what it is used for

Nerlynx is authorised as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HR+ HER2-overexpressed/amplified BC who completed adjuvant trastuzumab-based therapy less than one year ago. It contains neratinib as the active substance and it is given orally.

Further information about the evaluation of Nerlynx's benefits can be found in Nerlynx's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/medicines/human/EPAR/nerlynx

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nerlynx, together with measures to minimise such risks and the proposed studies for learning more about Nerlynx's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Nerlynx, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks

Important risks of Nerlynx are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nerlynx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Table II.A.1: List of important risks

Important identified risks	• Gastrointestinal toxicity - Diarrhoea • Hepatotoxicity
Important potential risks	• Cardiotoxicity - LVEF decreased • Pulmonary toxicity - Interstitial lung disease • Reproductive and developmental toxicity

Abbreviations: LVEF = left ventricular ejection fraction.

II.B Summary of important risks

Table II.B.2: Important risks

Important identified risk: Gastrointestinal toxicity - Diarrhoea	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment. Neratinib inhibits kinase activity through intracellular irreversible binding to a cysteine residue in the ATP binding pocket of the receptor and therefore can contribute to alterations in the growth and healing of the intestinal epithelium, as described in the potential mechanisms, causing diarrhoea.
Risk factors and risk groups	For diarrhoea in general, groups at risk include patients with significant chronic active inflammatory bowel disease or recent acute GI 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). Aggravating risk factors include concomitant medications and other predisposing conditions including advanced age.

Table II.B.2: Important risks

	For diarrhoea during treatment with TKIs, a small number of emerging clinical investigations have found an association between drug steady-state concentrations and diarrhoea, suggesting that gene variants within metabolic pathways for TKIs could play a role in toxicity susceptibility (Bowen, 2013).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL sections 2, 3, and 4 Additional risk minimisation measures: Provide patients and HPCs with educational material as additional resources to minimise diarrhoea.
Additional pharmacovigilance activities	PUMA-NER-6201 (CONTROL) – completed study. An open-label study to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and loperamide. Study PUMA-NER-6202 (DIANER) is being planned to evaluate the incidence of discontinuations due to diarrhoea at three cycles in patients with early-stage HER2-positive, hormone-receptor-positive BC treated with neratinib plus loperamide prophylaxis *versus* neratinib with initial dose escalation plus as-needed loperamide *versus* neratinib plus loperamide plus colesevelam prophylaxis. An observational ongoing study, NER-7402 (Nerlyfe), aims to describe the incidence of discontinuation due to diarrhoea within the first 3 months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and effectiveness of Nerlynx EMs. The study will also evaluate the use of antidiarrhoeal medication among new users of Nerlynx, assess the effectiveness of Nerlynx therapy on QoL, and further assess and characterize events of hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (ILD), reproductive and developmental toxicity. See Part II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical, and post-authorisation experience with neratinib treatment. Neratinib is an orally available, irreversible inhibitor of the EGFR, ERBB2, and ERBB4 receptors at the intracellular tyrosine kinase domains, and as such, a rigorous evaluation of TEAEs indicative

Table II.B.2: Important risks

	of hepatic injury and laboratory evaluations of liver function for potential DILI due to a potential class effect was conducted. Nonclinical studies with neratinib did not show significant hepatotoxicity. Minimal vacuolation was noted primarily in rats on biliary epithelial cells and was considered on-target and non-adverse. Slight increases in ALT and AST, and slight to mild reversible hepatic inflammation and/or necrosis were observed at high doses in dose range-finding studies. Due to the potential for a drug class effect of hepatotoxicity and as a precaution typically applied to clinical studies of an agent that has not been widely administered in the clinical setting, eligibility criteria for all neratinib trials in this data discussion excluded patients with baseline moderate hepatic dysfunction and in applicable trials, extensive hepatic metastases (more than one-third of the liver).
Risk factors and risk groups	Risk factors for DILI include increasing age, human immunodeficiency virus /acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic hepatitis B or C infection, obesity, and non-alcoholic fatty liver disease. Patients taking anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk (Bell et al, 2009). Severe toxic effects can be increased when TKIs are taken with a CYP3A4 inhibitor (Spraggs et al, 2013; Shah et al, 2013).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4. SmPC Section 4.8. PL Section 2 and 4 Additional risk minimisation measures: None

Important potential risk: Cardiotoxicity - LVEF decreased	
Evidence for linking the risk to the medicine	While nonclinical and clinical studies did not indicate a cardiotoxic effect from neratinib, decreases in LVEF were identified for similar compounds. Other agents in the same pharmacological class of TKIs that target ERBB2, have a cardiac toxicity profile reported in the product labelling. Cardiotoxicity (LVEF decreased) is considered as class effect.
Risk factors and risk groups	Cardiovascular side effects of TKIs are varied and have included heart failure, left ventricular dysfunction, conduction abnormalities, QT prolongation, acute coronary syndromes, myocardial injury, arterial thromboses, and hypertension. Overall, systolic dysfunction with resultant heart failure is one of

	the most common important side effects of TKI treatment (Chen et al, 2008). According to the American College of Cardiology and the American Heart Association, patients at high risk for developing heart failure are those with hypertension, coronary artery disease, diabetes mellitus, family history of cardiomyopathy, use of cardiotoxins, and obesity, who have no structural heart disease at present. Patients with asymptomatic heart failure but with structural heart disease (previous myocardial infarction, left ventricular remodelling including left ventricular hypertrophy and low ejection fraction, or asymptomatic valvular disease) are at risk of further left ventricular remodelling leading to development of heart failure symptoms. Treatment with anthracycline chemotherapy has been associated with a cumulative dose-dependent decrease in LVEF, which were asymptomatic for the most part. This progressive cardiotoxicity usually occurs after the completion of treatment with anthracyclines and may become apparent within one year of the completion of treatment (early onset chronic cardiotoxicity) or many years after chemotherapy has been completed (late onset chronic cardiotoxicity). Other risk factors have been identified that increase the risk of anthracycline-induced cardiotoxicity, such as concomitant treatment with cyclophosphamide, trastuzumab, or paclitaxel. The interaction between anthracyclines, such as doxorubicin, and trastuzumab, is of particular interest, given the relatively common use of the latter agent for adjuvant therapy for BC (Volkova and Russell, 2011).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: none
Important potential risk: Pulmonary toxicity- Interstitial lung disease	
Evidence for linking the risk to the medicine	Pulmonary toxicity, including pneumonitis, interstitial lung disease (ILD), and pulmonary fibrosis, is a known side effect of TKIs that target EGFR (Liu et al, 2007). TKI-associated toxicity generally occurs early after initiation of therapy; in 75% of cases of TKI-associated pulmonary toxicity, the complications occur within 3 months of initiation of drug use and the majority occurs within 4 weeks (Min et al, 2011). In preclinical studies of neratinib, no pulmonary toxicity was observed. Pulmonary toxicity, incl. ILD is considered as a class effect.
Risk factors and risk groups	As in cases associated with conventional antineoplastic drugs, pre-existing pulmonary fibrosis has been regarded as a risk

	factor for the development of ILD in targeted therapy. Other risk factors include male sex, a history of smoking, poor functional status, concomitant radiation therapy, absence of chemotherapy history, and a reduction in serum albumins (Min et al, 2011).
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none
Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Non-clinical experience.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Additional risk minimisation measures: None

Abbreviations: AE = adverse event; ALP = alkaline phosphatase ALT = alanine aminotransferase; AST = aspartate aminotransferase; (AT) = aminotransferase; BC = breast cancer; CT = computerised tomography; DILI = drug-induced liver injury; ECHO = echocardiogram; GI = gastrointestinal; HCO = health care provider; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; L+C = lapatinib plus capecitabine; LVEF =left ventricular ejection fraction; MUGA = multigated acquisition scan; PL =Package leaflet; QoL = quality of life; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no post-authorisation safety trial category 1 or 2 or efficacy studies planned.

II.C.2 Other studies in post-authorisation development plan

Study PUMA-NER-6201 (CONTROL) was conducted to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab. This study is completed.

Study PUMA-NER-6202 (DIANER) aims to evaluate the incidence of discontinuations due to diarrhoea at three cycles in patients with early-stage HER2-positive, hormone-receptor-positive BC treated with neratinib plus loperamide prophylaxis *versus* neratinib with initial dose escalation plus as-needed loperamide *versus* neratinib plus loperamide plus colesevelam prophylaxis. This study is planned.

An observational ongoing trial (NER-7402) aims to describe the incidence of discontinuation due to diarrhoea within the first three months of treatment with neratinib, in adult BC patients treated in extended adjuvant in a real-world setting, and to evaluate the availability, interpretability, and effectiveness of Nerlynx EMs. The trial will also evaluate the use of antidiarrhoeal medication among new users of Nerlynx, to assess the effectiveness of Nerlynx therapy on QoL.