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 HRc+ 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 1: List of important risks

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

Abbreviations: LVEF = left ventricular ejection fraction.
[a] Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering.

II.B Summary of important risks

Table 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.
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. 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 (Annex 6).

Table 2: Important risks

Additional pharmacovigilance activities	PUMA-NER-6201. 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 is being planned to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide. An observational study, NER-7402 (Nerlyfe), is being planned 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 antidiarrheal 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: Gastrointestinal Toxicity - Stomatitis	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
Risk factors and risk groups	Among patient-related risk factors, comorbidities such as malnutrition and poor oral health can contribute relevantly to the risk of oral mucositis (stomatitis) (Seiler et al, 2014).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8. PL section 4 Additional risk minimisation measures: None
Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
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).

Table 2: Important risks

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	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
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	Non-clinical, clinical, and post-authorisation experience with neratinib treatment.
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; N+C = neratinib plus capecitabine; N+D = neratinib plus digoxin; N+F = neratinib plus fulvestrant; N+F+T = neratinib plus fulvestrant plus trastuzumab; N+P = neratinib plus paclitaxel; N+T = neratinib plus trastuzumab; N+TS = neratinib plus temsirolimus; N+V = neratinib plus vinorelbine; PL =; 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 is being 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.

Study PUMA-NER-6202 is being planned to characterize the incidence and severity of diarrhoea in patients with early-stage HER2+ BC treated with neratinib and intensive loperamide prophylaxis versus initial dose escalation plus as-needed loperamide in the first month of treatment.

An observational trial (NER-7402) is being planned 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 antidiarrheal medication among new users of Nerlynx, to assess the effectiveness of Nerlynx therapy on QoL.