Nerlynx

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0033	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	31/05/2023	n/a		
R/0031	Renewal of the marketing authorisation.	30/03/2023	26/05/2023	SmPC, Annex II, Labelling	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

				and PL	Nerlynx in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0032	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/04/2023	n/a		
PSUSA/10712 /202207	Periodic Safety Update EU Single assessment - neratinib	09/02/2023	n/a		PRAC Recommendation - maintenance
II/0029	Update of section 5.2 of the SmPC in order to add information on distribution and on the effect of neratinib on CYP substrates based on non-clinical studies XT218036 and 20325317; Study XT218036 was designed to evaluate neratinib as a substrate of the human transporters OATP1B1 and OATP1B3 and study 20325317 objective was to determine the inactivation kinetic constants (kinact and KI) of Neratinib and M6 for the human cytochrome P450 (CYP) isoenzymes 2B6 and 3A4 using pooled human liver microsomes (HLM). In addition, MAH is also taking this opportunity to introduce editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2022	26/05/2023	SmPC	In vitro studies demonstrated that neratinib and its main metabolite M6 are not substrates of hepatic uptake transporters OATP1B1*1a and OATP1B3 at relevant clinical concentration. Neratinib and metabolite M6 were not potent direct inhibitors of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4 and no time-dependent inhibition is expected. For more information, please refer to the Summary of Product Characteristics.
II/0027	Submission of the final results from study PUMA-NER-6201 (CONTROL), listed as a category 3 study in the RMP; this is an Open-Label Study to	23/06/2022	n/a		

	Characterize the Incidence and Severity of Diarrhea in Patients with Early Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide. The RMP version 3.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10712 /202107	Periodic Safety Update EU Single assessment - neratinib	24/02/2022	25/04/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10712/202107.
IAIN/0028	A.1 - Administrative change - Change in the name and/or address of the MAH	24/01/2022	25/04/2022	SmPC, Labelling and PL	
IA/0026	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/10/2021	n/a		
IA/0024	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	16/09/2021	n/a		
PSUSA/10712 /202101	Periodic Safety Update EU Single assessment - neratinib	02/09/2021	n/a		PRAC Recommendation - maintenance
II/0021	Update of sections 5.3 and 6.6 of the SmPC based on an updated environmental risk assessment including	02/09/2021	25/10/2021	SmPC	Environmental risk assessment studies have shown that neratinib has an evident potential to be persistent,

	ERA studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				bioaccumulative, and toxic to the environment. This medicinal product may pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
IA/0023	To change the ATC Code of neratinib from L01XE45 to L01EH02. A.6 - Administrative change - Change in ATC Code/ATC Vet Code	19/05/2021	25/10/2021	SmPC	
II/0020	Submission of a revised RMP version 1.2 in order to update data concerning post authorization safety studies and to change the submission date of the final Study Report of PASS n°6201, from Q1 2021 to Q4 2021. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	09/04/2021	n/a		Nerlynx RMP was revised in order to update data from post-authorisation safety studies and to change the date of the submission of the final CSR of the PASS n°6201 (from Q12021 to Q4 2021). RMP version 1.2 was approved.
PSUSA/10712 /202007	Periodic Safety Update EU Single assessment - neratinib	11/02/2021	n/a		PRAC Recommendation - maintenance
IB/0019	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time	24/11/2020	n/a		

	data				
IA/0018	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	04/11/2020	n/a		
IB/0017	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/10/2020	n/a		
II/0015	Update of section 5.1 of the SmPC in order to include final OS results from study 3144A2-3004-WW, a randomised, double-blind, placebo-controlled trial of neratinib after trastuzumab in women with early-stage HER-2/neu overexpressed/amplified breast cancer. The MAH has also taken the opportunity to make some corrections in the SmPC and package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/10/2020	25/10/2021	SmPC and PL	The median OS follow-up time in study 3144A2-3004-WW was 8.03 years in the neratinib arm and 8.10 years in the placebo arm, with 746 (52.5%) patients in the neratinib arm and 796 (56.1%) patients in the placebo arm followed up for survival for 8 or more years. The number of deaths was 127 (8.9%) in the patients treated with neratinib and 137 (9.6%) in the patients treated with placebo. There was no statistically significant difference in overall survival between the Nerlynx and the placebo arm [HR 0.96 (95% CI: 0.75, 1.22)] in the ITT population at a median follow-up of 8.06 years. In the hormone receptor positive population who were less than one year from completion of trastuzumab therapy, the median follow-up was 8.0 years in the neratinib arm and 8.1 years in the placebo arm, with 671 (23.6%) patients in the neratinib arm and 668 (23.5%) patients in the placebo arm followed up for survival for 8 or more years. In this

					subpopulation the number of deaths was 55 (8.2%) in the patients treated with neratinib and 68 (10.2%) in the patients treated with placebo [HR 0.83 (95% CI, 0.58, 1.18)]. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10712 /202001	Periodic Safety Update EU Single assessment - neratinib	03/09/2020	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. Update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC in order to update the pharmacokinetics properties of neratinib and amend drug-drug interaction (DDI) information with CYP3A4/P-gp inducers and inhibitors based on two ADME studies (PUMA-NER-0105 and PUMA-NER-0102), a PBPK model report and in vitro studies; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor corrections to the PI and to bring the PI in line with the latest QRD template version 10 and SmPC Guideline. Update of sections 4.2, 4.3, 4.4, 4.5 and 5.2 of the SmPC in order to update DDI information with H2-receptor antagonists and add DDI information with loperamide based on two DDI studies (PUMA-NER-0104, PUMA-NER-0103); the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/06/2020	27/07/2020	SmPC and PL	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, Nerlynx dose adjustment should be applied. Nerlynx dose should be reduced to 40 mg taken once daily with a strong CYP3A4/P-gp inhibitor. Nerlynx dose should be reduced to 40 mg taken once daily with a moderate CYP3A4/P-gp. If well tolerated, the dose can be increased to 80 mg for at least 1 week, then to 120 mg for at least 1 weeks, and to 160 mg as a maximal daily dose. Patient should be monitored carefully, especially GI effect including diarrhoea and hepatotoxicity. After discontinuation of a strong or moderate CYP3A4/P-gp inhibitor, the previous dose of Nerlynx 240 mg can be resumed. Concomitant treatment with moderate CYP3A4 and P-gp inducer is not recommended as it may lead to a loss of neratinib efficacy. Co-administration with the following medical products that are strong inducers of the CYP3A4/P-gp isoform of cytochrome P450 is contraindicated: carbamazepine, phenytoin (antiepileptics); St John's wort (Hypericum perforatum) (herbal product); rifampicin (antimycobacterial).

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Treatments that increase gastrointestinal pH may lower the absorption of neratinib, thus decreasing systemic exposure. In case of H2-receptor antagonists modalities of administration should be adapted. Nerlynx should be taken at least 2 hours before or 10 hours after the intake of the H2-receptor antagonist.
II/0014/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/07/2020	n/a		
IB/0013	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	28/04/2020	n/a		
PSUSA/10712 /201907	Periodic Safety Update EU Single assessment - neratinib	13/02/2020	n/a		PRAC Recommendation - maintenance
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/01/2020	27/07/2020	Labelling	
IB/0009	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/01/2020	n/a		
II/0007	Update of section 5.1 of the SmPC to update the results of the multicentre, randomised, double-blind,	12/12/2019	27/07/2020	SmPC	Re-analyses were conducted with the corrected stratification factors using case report form (CRF)

	placebo-controlled, pivotal phase III study, ExteNET (3004) in women with early-stage HER2-positive breast cancer who had completed adjuvant treatment with trastuzumab, based on a re-analysis conducted with corrected stratification factors. Furthermore, the MAH took the opportunity to make some corrections in section 4.4 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				stratification variables, instead of Interactive Response Technology (IRT) variables. The stratification discrepancies between the IRT and CRF data did not lead to imbalance between the treatment arms that could have caused potential bias, nor did they impact the validity of the study conclusions, as the re-analyses results were similar to the results with the per protocol IRT variables.
IAIN/0006/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	02/10/2019	27/07/2020	SmPC, Annex II, Labelling and PL	

IB/0004	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	27/09/2019	27/07/2020	SmPC, Labelling and PL	
IB/0005/G	This was an application for a group of variations. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	19/09/2019	n/a		
PSUSA/10712 /201901	Periodic Safety Update EU Single assessment - neratinib	11/07/2019	n/a		PRAC Recommendation - maintenance
T/0003	Transfer of Marketing Authorisation	11/06/2019	04/07/2019	SmPC, Labelling and PL	
T/0001	Transfer of Marketing Authorisation	15/03/2019	28/03/2019	SmPC, Labelling and PL	