



Enhertu

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
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2025	n/a		
II/0048	Extension of indication to include treatment of adult patients with unresectable or metastatic HER2-low or	27/02/2025	31/03/2025	SmPC, Annex II, Labelling	Please refer to Scientific Discussion 'Enhertu-H-C-005124-II-48'.

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).



	<p>HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment for ENHERTU, based on results from study D9670C00001 (DESTINY-Breast06); this is a phase 3, randomized, multicentre, open-label study of trastuzumab deruxtecan (DS-8201a) compared with investigator's choice chemotherapy in, hormone receptor-positive, HER2-low and HER2-ultralow BC patients whose disease has progressed on endocrine therapy in the metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI, and to update the PI according to the Excipients Guideline. Furthermore, the PI is brought in line with the latest QRD template version 10.4.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>			and PL	
PSUSA/10894 /202406	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	30/01/2025	24/03/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s) for PSUSA/10894/202406.
II/0051	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	12/12/2024	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method				
IA/0053/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	02/12/2024	24/03/2025	Annex II	
IB/0052	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/11/2024	n/a		
R/0047	Renewal of the marketing authorisation.	19/09/2024	28/10/2024		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Enhertu, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0050	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	16/10/2024	24/03/2025	SmPC and PL	
PSUSA/10894 /202312	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	11/07/2024	n/a		PRAC Recommendation - maintenance

IB/0046	B.I.z - Quality change - Active substance - Other variation	24/04/2024	n/a		
II/0043/G	This was an application for a group of variations. B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs	18/04/2024	n/a		
IB/0045/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	25/03/2024	n/a		
II/0040	Update of sections 4.2 and 5.2 of the SmPC based on the final results from studies DS8201-A-J101, DS8201-A-J102, DS8201-A-A103, DS8201-A-A104, DS8201-A-U201, DS8201-A-J202, DS8201-A-J203, DS8201-A-U204, DS8201-A-U205, DS8201-A-U206,	11/01/2024	16/09/2024	SmPC	Sections 4.2 and 5.2 of the SmPC are being updated to replace the qualifier 'insufficient' by 'limited' when referring to available data pertaining to hepatic impairment and specifically patients with total bilirubin > 1.5 to 3 times

	<p>DS8201-A-U207, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303, in order to fulfil MEA 002 (a collection of PK and safety data in at least 10 subjects with moderate hepatic impairment from ongoing Phase 2 or 3 clinical studies) listed as a category 3 activity in the RMP. The updated RMP version 8.0 has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes to the SmPC, annex II.D and the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				ULN, irrespective of AST level.
PSUSA/10894 /202306	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	11/01/2024	n/a		PRAC Recommendation - maintenance
II/0036	<p>Submission of the final study report from non-imposed non-interventional PASS 'EU survey of relevant healthcare professionals on understanding of key risk minimisations measures pertaining to ILD/pneumonitis' in order to fulfil MEA 003.2, a category 3 study listed in the RMP.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	11/01/2024	n/a		<p>The final report for non-imposed non-interventional PASS 'EU survey of relevant healthcare professionals on understanding of key risk minimisations measures pertaining to ILD/pneumonitis' in order to fulfil MEA 003.2, a category 3 study listed in the RMP was submitted as part of this variation application. The primary objective of the study was to assess physicians' awareness, knowledge, and implementation of risk minimization measures related to the risk, early detection, diagnosis, and management of ILD/pneumonitis. The primary outcome of the risk minimization measures was evaluated as effective if all the following success criteria were met: the proportion of physicians being aware of the risk of ILD/pneumonitis was 80% or greater, the proportion of physicians</p>

					knowledgeable about the risk of ILD/pneumonitis was 60% or greater, and the proportion of physicians answering the implementation questions correctly was 75% or greater. Overall, the study was well conducted, but the primary outcome regarding risk minimization measures effectiveness was not met. Nevertheless, the MAH did provide satisfactory justification as to why this was not achieved, mainly in the knowledge domain. Overall, the risk of ILD/pneumonitis should remain as an imported identified risk as well as the applicable additional risk minimization measures (HCP Guide and Patient Card) in the RMP for Enhertu.
IA/0042	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	30/11/2023	n/a		
IA/0041	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	30/11/2023	n/a		
R/0035	Renewal of the marketing authorisation.	14/09/2023	24/10/2023		
II/0027	Extension of indication to include the indication treatment of non-small cell lung cancer (NSCLC) for Enhertu (trastuzumab deruxtecan), based on results from study DS8201-A-U206 (DESTINY-Lung02), a phase 2, randomised study evaluating the safety and efficacy of trastuzumab deruxtecan in subjects with HER2-mutated metastatic non-small cell lung cancer.	14/09/2023	18/10/2023	SmPC and PL	Please refer to Scientific Discussion Enhertu -H-C-005124-II-0027.

	<p>As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 7.0 of the RMP has also been submitted. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>				
II/0037	<p>Submission of the final clinical study report addendum for study DS8201-A-U303 (DESTINY-Breast04) in order to fulfil the recommendation to submit the final OS analysis. U303 is a phase 3, multicentre, randomised, open-label, active-controlled trial of trastuzumab deruxtecan (T-DXd), an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p>	12/10/2023	16/09/2024	SmPC	<p>SmPC new text</p> <p>Updated efficacy results have been provided for study DS8201-A-U303 DESTINY-Breast04 (NCT03734029) in 5.1 Pharmacodynamic properties. Final analysis of data with a new data cut-off (DCO) date of 01 Mar 2023 are presented and the median follow-up time is now 32 months. The primary analysis K-M Curve has also been replaced with the updated latest OS update K-M graph.</p> <p>For more information, please refer to the Summary of Product Characteristics.</p>
IAIN/0039	<p>B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer</p>	21/09/2023	n/a		

II/0031	<p>Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update safety, efficacy and pharmacokinetic information based on data from study DS8201-A-U301 and study DS8201-A-U302. Study U301 was a Phase 3, randomized, 2-arm, open-label, multicenter study designed to compare the safety and efficacy of T-DXd vs TPC in HER2-positive, unresectable and/or metastatic BC subjects who were resistant or refractory to T-DM1. Study U302 was a Phase 3, multicenter, randomized, open-label, 2-arm, active-controlled study in subjects with unresectable and/or metastatic HER2-positive (IHC 3+ or ISH-positive) BC previously treated with trastuzumab plus taxane in the advanced/metastatic setting or who had progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab plus taxane. The Package Leaflet and Annex II are updated accordingly. The RMP has also been updated (version 5.0).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	06/07/2023	18/10/2023	SmPC, Annex II and PL	<p>SmPC new text</p> <ul style="list-style-type: none"> In section 4.8 Undesirable effects: update of pooled safety population data for Enhertu 5.4 mg/kg, update of Table 3: Adverse reactions in patients treated with trastuzumab deruxtecan 5.4 mg/kg and 6.4 mg/kg in multiple tumour types (by system organ class and frequency category), update of data of selected adverse reactions, based on data from study DS8201-A-U301 and study DS8201-A-U302 In section 5.1 Pharmacodynamic properties: editorial changes, update of data for DESTINY-Breast03 including Table 4: Efficacy results in DESTINY-Breast03, addition of data from DESTINY-Breast02, In section 5.2 Pharmacokinetic properties: update of pharmacokinetic data for volume of distribution, elimination and linearity / non-linearity. <p>For more information, please refer to the Summary of Product Characteristics.</p>
PSUSA/10894 /202212	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0034	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/05/2023	n/a		

II/0030	<p>Update of sections 4.8 and 5.1 of the SmPC in order to update transfusion data for subjects with human epidermal growth factor receptor 2 (HER2)-positive GC or GEJ adenocarcinoma and to update the overall response rate for study DS8201-A-J202 (following the assessment of procedure II/0012) based on studies DS8201-A-J101, DS8201-A-J202 (DESTINY-Gastric01) and DS8201-A-U205 (DESTINY-Gastric02).</p> <p>DS8201-A-J101 is a Phase 1, Two-part, Multicentre, Non-randomised, Open-label, Multiple Dose First-in-Human Study in Advanced Solid Malignant Tumour. DS8201-A-J202 is a Phase 2, Multicentre, Open-label Study of DS-8201a in Subjects with HER2-Expressing Advanced GC/GEJ Adenocarcinoma.</p> <p>DS8201-A-U205 is a Phase 2, Multicentre, Open-label, Single-arm Trial of Trastuzumab Deruxtecan in HER2-Positive, Unresectable or Metastatic GC or GEJ Adenocarcinoma Subjects who have progressed on or after a Trastuzumab-containing Regimen.</p> <p>In addition, the MAH took this opportunity to implement minor editorial changes to the SmPC.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	25/05/2023	18/10/2023	SmPC	<p>SmPC new text</p> <ul style="list-style-type: none"> • In section 4.8 Undesirable effects <ul style="list-style-type: none"> o Update of the proportion of GC/GEJ patients who received transfusion from 22.7% (solely concomitant medication) to 25.3% (concomitant medication and as non-drug therapy/procedure) within 28 days after onset of anaemia or thrombocytopenia. o Editorial changes to tables footnotes <p>In section 5.1 Pharmacodynamic properties: update of the ORR for Study DESTINY-Gastric01 (J202) from 40.5% to 39.7% based on the latest data cut off analysis of 03 June 2020. This correction also updates the figures for the other endpoints OS, median DoR and PFS, based on the same data cut off of 03 June 2020. For more information, please refer to the Summary of Product Characteristics.</p>
IB/0032	<p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p>	04/05/2023	n/a		

IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	19/04/2023	n/a		
IB/0028/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	23/03/2023	n/a		
II/0022	<p>Extension of indication to include treatment of unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or withing 6 months of completing adjuvant chemotherapy; for ENHERTU, based on final results from study DS8201-A-U303 (DESTINY-Breast04). This is a Phase III, multicentre, randomised, open-label, active-controlled trial of Trastuzumab Deruxtecan (T-DXd), an Anti-HER2-antibody Drug Conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects.</p> <p>As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.</p> <p>In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC to update the dosing recommendation for corticosteroid treatment (e.g. prednisolone) with a</p>	15/12/2022	23/01/2023	SmPC and PL	Please refer to Scientific Discussion 'Enhertu-H-C-005124-II-22'

	<p>daily dose.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>				
PSUSA/10894 /202206	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	12/01/2023	n/a		PRAC Recommendation - maintenance
II/0012	<p>Extension of indication to include monotherapy treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen for Enhertu based on final results from studies DS8201-A-U205 (DESTINY Gastric02) and DS8201 A J202 (DESTINY Gastric01); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Annex II and the Package Leaflet is updated in accordance. In addition, changes regarding the dosing recommendation for corticosteroid treatment and the protection of the infusion bag from light have been introduced. Version 3.0 of the RMP has also been submitted.</p> <p>The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>	10/11/2022	12/12/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion Enhertu II-0012

IB/0026	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2022	12/12/2022	SmPC, Labelling and PL	
R/0023	Renewal of the marketing authorisation.	15/09/2022	28/10/2022	SmPC and Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Enhertu, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0019	Update of section 4.2 of the SmPC to add nausea/vomiting premedication prophylaxis information following procedure II/14 based on analyses from Study DS8201-A-U302 (DESTINY-Breast03); this is a Phase 3, multicenter, randomized, open-label, 2-arm, active controlled study in subjects with unresectable and/or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane. 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 data	21/07/2022	25/08/2022	SmPC, Annex II and PL	SmPC new text Enhertu is emetogenic (see SmPC section 4.8), which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting. For more information, please refer to the Summary of Product Characteristics.
IB/0024	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall	08/08/2022	n/a		

	quality of the AS				
IB/0021	B.II.d.z - Change in control of the Finished Product - Other variation	11/07/2022	n/a		
II/0014	<p>Extension of indication for Enhertu to include treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>	23/06/2022	11/07/2022	SmPC and PL	Please refer to Scientific Discussion 'Enhertu II-0014'
PSUSA/10894 /202112	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	07/07/2022	n/a		PRAC Recommendation - maintenance
IB/0020	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	07/06/2022	11/07/2022	SmPC	
IB/0017	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	22/04/2022	11/07/2022	SmPC, Annex II and PL	
IB/0018	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a	13/04/2022	n/a		

	biological/immunological medicinal product				
II/0010	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	03/03/2022	n/a		
IA/0015	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	09/02/2022	11/07/2022	SmPC	
IB/0013	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/01/2022	n/a		
II/0009	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	20/01/2022	n/a		
PSUSA/10894 /202106	Periodic Safety Update EU Single assessment - trastuzumab deruxtecan	13/01/2022	n/a		PRAC Recommendation - maintenance
II/0005/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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/11/2021	n/a		
R/0006	Renewal of the marketing authorisation.	16/09/2021	12/11/2021	Annex II and	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and

				PL	having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Enhertu, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0004	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	24/08/2021	n/a		
IB/0008/G	<p>This was an application for a group of variations.</p> <p>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits</p> <p>B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits</p> <p>B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits</p>	20/08/2021	n/a		

IAIN/0007	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	14/07/2021	n/a		
IB/0002/G	This was an application for a group of variations. 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 B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	07/06/2021	n/a		
IAIN/0003	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	21/05/2021	n/a		
IB/0001	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	30/04/2021	12/11/2021	SmPC, Annex II, Labelling and PL	