

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Enhertu 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution contains 20 mg/mL of trastuzumab deruxtecan (see section 6.6).

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) that contains a humanised anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, produced by mammalian (Chinese Hamster Ovary) cells, covalently linked to DXd, an exatecan derivative and a topoisomerase I inhibitor, via a tetrapeptide-based cleavable linker. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to yellowish-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

4.2 Posology and method of administration

Enhertu should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products. In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Enhertu should not be substituted with trastuzumab or trastuzumab emtansine.

Patients treated with trastuzumab deruxtecan should have documented HER2-positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by *in situ* hybridization (ISH) or by fluorescence *in situ* hybridization (FISH) assessed by a CE-marked *in vitro* diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test.

Posology

The recommended dose of Enhertu is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions. Antiemetics may be administered in accordance with local medical practice as per patient tolerance for prophylaxis or management.

The infusion rate of Enhertu should be slowed or interrupted if the patient develops infusion-related symptoms. Enhertu should be permanently discontinued in case of severe infusion reactions.

Dose modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of Enhertu per guidelines provided in Tables 1 and 2.

Enhertu dose should not be re-escalated after a dose reduction is made.

Table 1: Dose reduction schedule

Dose reduction schedule (Starting dose is 5.4 mg/kg)	Dose to be administered
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2: Dose modifications for adverse reactions

Adverse reaction	Severity	Treatment modification
Interstitial lung disease (ILD)/pneumonitis	Asymptomatic ILD/pneumonitis (Grade 1)	Interrupt Enhertu until resolved to Grade 0, then: <ul style="list-style-type: none">• if resolved in 28 days or less from date of onset, maintain dose.• if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1).• consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section 4.4).
	Symptomatic ILD/pneumonitis (Grade 2 or greater)	<ul style="list-style-type: none">• Permanently discontinue Enhertu.• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see section 4.4).
Neutropenia	Grade 3 (less than $1.0-0.5 \times 10^9/L$)	<ul style="list-style-type: none">• Interrupt Enhertu until resolved to Grade 2 or less, then maintain dose.
	Grade 4 (less than $0.5 \times 10^9/L$)	<ul style="list-style-type: none">• Interrupt Enhertu until resolved to Grade 2 or less.• Reduce dose by one level (see Table 1).
Febrile neutropenia	Absolute neutrophil count of less than $1.0 \times 10^9/L$ and temperature greater than 38.3 °C or a sustained temperature of 38 °C or greater for more than one hour.	<ul style="list-style-type: none">• Interrupt Enhertu until resolved.• Reduce dose by one level (see Table 1).

Adverse reaction	Severity		Treatment modification
Left ventricular ejection fraction (LVEF) decreased	LVEF greater than 45% and absolute decrease from baseline is 10% to 20%		<ul style="list-style-type: none"> Continue treatment with Enhertu.
	LVEF 40% to 45%	And absolute decrease from baseline is less than 10%	<ul style="list-style-type: none"> Continue treatment with Enhertu. Repeat LVEF assessment within 3 weeks.
		And absolute decrease from baseline is 10% to 20%	<ul style="list-style-type: none"> Interrupt Enhertu. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue Enhertu. If LVEF recovers to within 10% from baseline, resume treatment with Enhertu at the same dose.
	LVEF less than 40% or absolute decrease from baseline is greater than 20%		<ul style="list-style-type: none"> Interrupt Enhertu Repeat LVEF assessment within 3 weeks. If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue Enhertu.
	Symptomatic congestive heart failure (CHF)		<ul style="list-style-type: none"> Permanently discontinue Enhertu.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

Delayed or missed dose

If a planned dose is delayed or missed, it should be administered as soon as possible without waiting until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion should be administered at the dose and rate the patient tolerated in the most recent infusion.

Special populations

Elderly

No dose adjustment of Enhertu is required in patients aged 65 years or older. Limited data are available in patients ≥ 75 years of age.

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance [CL_{Cr}] ≥ 60 and < 90 mL/min) or moderate (CL_{Cr} ≥ 30 and < 60 mL/min) renal impairment (see section 5.2). The potential need for dose adjustment in patients with severe renal impairment cannot be determined due to insufficient data. A higher incidence of Grade 1 and 2 ILD has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with total bilirubin ≤ 1.5 times upper limit of normal (ULN), irrespective of aspartate transaminase (AST) value. The potential need for dose adjustment in

patients with total bilirubin > 1.5 times ULN, irrespective of AST value, cannot be determined due to insufficient data; therefore, these patients should be monitored carefully (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Enhertu in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

Enhertu is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Enhertu must not be administered as an intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Interstitial lung disease/pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with Enhertu (see section 4.8). Fatal outcomes have been observed. Patients should be advised to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD/pneumonitis. Evidence of ILD/pneumonitis should be promptly investigated. Patients with suspected ILD/pneumonitis should be evaluated by radiographic imaging, preferably a computed tomography (CT) scan. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g. ≥ 0.5 mg/kg prednisolone or equivalent). Enhertu should be withheld until recovery to Grade 0 and may be resumed according to instructions in Table 2 (see section 4.2). For symptomatic ILD/pneumonitis (Grade 2 or greater), promptly initiate corticosteroid treatment (e.g. ≥ 1 mg/kg prednisolone or equivalent) and continue for at least 14 days or until complete resolution of clinical and chest CT findings. Then gradually taper for at least 4 weeks. Enhertu should be permanently discontinued in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD/pneumonitis (see section 4.2). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Neutropenia

Cases of neutropenia, including febrile neutropenia, were reported in clinical studies of Enhertu. Complete blood counts should be monitored prior to initiation of Enhertu and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, Enhertu may require dose interruption or reduction (see section 4.2).

Left ventricular ejection fraction decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received Enhertu 5.4 mg/kg, three cases (1.3%) of asymptomatic LVEF decrease, of which 2 (0.9%) were Grade 2 and 1 (0.4%) was Grade 3, were reported. Observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or multigated acquisition [MUGA] scanning) was 37 (16.9%); all were Grade 2. No decreases of LVEF to less than 40% or absolute decrease from baseline of greater than 20% were observed. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment (see section 4.8).

Standard cardiac function testing (echocardiogram or MUGA scanning) should be performed to assess LVEF prior to initiation of Enhertu and at regular intervals during treatment as clinically indicated. Enhertu should be permanently discontinued if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (see section 4.2).

Embryo-foetal toxicity

Enhertu can cause foetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab, a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can also cause embryo-foetal harm when administered to a pregnant woman (see section 4.6).

The pregnancy status of females of reproductive potential should be verified prior to the initiation of Enhertu. The patient should be informed of the potential risks to the foetus. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Enhertu and for at least 4 months after the last dose of Enhertu (see section 4.6).

Patients with moderate or severe hepatic impairment

There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. As metabolism and biliary excretion are the primary routes of elimination of the topoisomerase I inhibitor, DXd, Enhertu should be administered with caution in patients with moderate and severe hepatic impairment (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration with ritonavir, an inhibitor of OATP1B, CYP3A and P-gp, or with itraconazole, a strong inhibitor of CYP3A and P-gp, resulted in no clinically meaningful (approximately 10-20%) increase in exposures of trastuzumab deruxtecan or the released topoisomerase I inhibitor, DXd. No dose adjustment is required during co-administration of trastuzumab deruxtecan with medicinal products that are inhibitors of CYP3A or OATP1B or P-gp transporters (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status of women of childbearing potential should be verified prior to initiation of Enhertu.

Women of childbearing potential should use effective contraception during treatment with Enhertu and for at least 7 months following the last dose.

Men with female partners of childbearing potential should use effective contraception during treatment with Enhertu and for at least 4 months following the last dose.

Pregnancy

There are no available data on the use of Enhertu in pregnant women. However, trastuzumab, a HER2 receptor antagonist, can cause foetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios in some cases manifested as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on findings in animals and its mechanism of action, the topoisomerase I inhibitor component of Enhertu, DXd, can be expected to cause embryo-foetal harm when administered to a pregnant woman (see section 5.3).

Administration of Enhertu to pregnant women is not recommended, and patients should be informed of the potential risks to the foetus before they become pregnant. Women who become pregnant must immediately contact their doctor. If a woman becomes pregnant during treatment with Enhertu or within 7 months following the last dose of Enhertu, close monitoring is recommended.

Breast-feeding

It is not known if trastuzumab deruxtecan is excreted in human milk. Human IgG is secreted in human milk, and the potential for absorption and serious adverse reactions to the infant is unknown. Therefore, women should not breast-feed during treatment with Enhertu or for 7 months after the last dose. A decision should be made to discontinue breast-feeding or to discontinue treatment taking into account the benefit of breast-feeding for the child and/or benefit of treatment with Enhertu for the mother.

Fertility

No dedicated fertility studies have been conducted with trastuzumab deruxtecan. Based on results from animal toxicity studies, Enhertu may impair male reproductive function and fertility. It is not known whether trastuzumab deruxtecan or its metabolites are found in seminal fluid. Before starting treatment, male patients should be advised to seek counselling on sperm storage. Male patients must not freeze or donate sperm throughout the treatment period, and for at least 4 months after the final dose of Enhertu.

4.7 Effects on ability to drive and use machines

Enhertu may have a minor influence on the ability to drive and use machines. Patients should be advised to use caution when driving or operating machinery in case they experience fatigue, headache or dizziness during treatment with Enhertu (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were nausea (79.9%), fatigue (60.3%), vomiting (48.7%), alopecia (46.2%), constipation (35.9%), decreased appetite (34.6%), anaemia (33.8%), neutropenia (32.5%), diarrhoea (30.8%), thrombocytopenia (23.1%), cough (21.4%), leukopenia (20.5%), and headache (20.1%).

The most common National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4.03) Grade ≥ 3 adverse reactions were neutropenia (18.8%), anaemia (9.0%), nausea (6.8%), fatigue (6.4%), leukopenia (5.6%), lymphopenia (5.1%), vomiting (4.3%), thrombocytopenia (4.3%), hypokalaemia (3.4%), interstitial lung disease (ILD, 3.0%), diarrhoea (2.6%), febrile neutropenia (1.7%), dyspnoea (1.7%), abdominal pain (1.3%), decreased appetite (1.3%), and alanine aminotransferase increased (1.3%). In 2.6% of patients, ILD led to death.

Dose interruptions due to adverse reactions occurred in 27% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (14.5%), anaemia (3.4%), upper respiratory tract infection (3.0%), leukopenia (3.0%), ILD (2.6%), thrombocytopenia (2.6%), and fatigue (2.1%). Dose reductions occurred in 15% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were fatigue (3.8%), nausea (3.4%), and neutropenia (3.4%). Discontinuation of therapy due to an adverse reaction occurred in 12% of patients treated with Enhertu. The most frequent adverse reaction associated with permanent discontinuation was ILD (9.4%).

Tabulated list of adverse reactions

The safety of Enhertu has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of Enhertu 5.4 mg/kg in clinical studies. The median duration of exposure to Enhertu was 9.8 months (range: 0.7 to 37.1 months).

The adverse reactions in patients who received at least one dose of Enhertu in clinical studies are presented in Table 3. The adverse reactions are listed by MedDRA system organ class (SOC) and categories of frequency. Frequency categories are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with trastuzumab deruxtecan

System organ class/preferred term or grouped term	Frequency
Infections and infestations	
Upper respiratory tract infection ^a	Very common
Blood and lymphatic system disorders	
Neutropenia ^b	Very common
Anaemia ^c	Very common
Leukopenia ^d	Very common
Lymphopenia ^e	Very common
Thrombocytopenia ^f	Very common
Febrile neutropenia	Common
Metabolism and nutrition disorders	
Hypokalaemia	Very common
Decreased appetite	Very common
Nervous system disorders	
Headache ^g	Very common
Dizziness	Very common
Eye disorders	
Dry eye	Very common
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease ^h	Very common

System organ class/preferred term or grouped term	Frequency
Dyspnoea	Very common
Cough	Very common
Epistaxis	Very common
Gastrointestinal disorders	
Nausea	Very common
Vomiting	Very common
Diarrhoea	Very common
Abdominal pain ⁱ	Very common
Constipation	Very common
Stomatitis ^j	Very common
Dyspepsia	Very common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Rash ^k	Very common
General disorders and administration site conditions	
Fatigue ^l	Very common
Investigations	
Alanine aminotransferase increased	Very common
Aspartate aminotransferase increased	Very common
Ejection fraction decreased ^m	Very common
Injury, poisoning and procedural complications	
Infusion-related reactions ⁿ	Common

^a Includes influenza, influenza-like illness, and upper respiratory tract infection.

^b Includes neutropenia and neutrophil count decreased.

^c Includes anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased.

^d Includes leukopenia and white blood cell count decreased.

^e Includes lymphopenia and lymphocyte count decreased.

^f Includes thrombocytopenia and platelet count decreased.

^g Includes headache, sinus headache, and migraine.

^h Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organising pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

ⁱ Includes abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

^j Includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

^k Includes rash, rash pustular, and rash maculopapular.

^l Includes fatigue and asthenia.

^m Includes laboratory parameters of LVEF decrease (n = 37) and/or preferred terms of ejection fraction decreased (n = 3), cardiac failure (n = 1) and cardiac failure congestive (n = 1).

ⁿ Cases of infusion-related reactions include infusion-related reaction (n = 4), hypersensitivity (n = 1), and flushing (n = 1).

Description of selected adverse reactions

Interstitial lung disease

In clinical studies (n = 234), ILD occurred in 15.0% of patients. Most ILD cases were Grade 1 (3.0%), Grade 2 (8.5%) or Grade 3 (0.4%). Grade 5 events occurred in 3.0% of patients. Median time to first onset was 5.5 months (range: 1.2 to 20.8) (see sections 4.2 and 4.4).

Neutropenia

In clinical studies (n = 234), a decrease in neutrophil count was reported in 32.5% of patients and 18.8% had Grade 3 or 4 events. Median time of onset was 53 days (range: 8 days to 18.0 months), and median duration of the first event was 22 days (range: 2 days to 9.0 months). Febrile neutropenia was reported in 1.7% of patients (see section 4.2).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 0.6% (4/640) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. There was no association between development of antibodies and allergic-type reactions.

Paediatric population

Safety has not been established in this population.

Elderly

Of the 234 patients with HER2-positive breast cancer treated with Enhertu 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (49%) as compared to younger patients (39%), leading to more discontinuations due to adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

The maximum tolerated dose of trastuzumab deruxtecan has not been determined. In clinical studies, single doses higher than 8.0 mg/kg have not been tested. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors, ATC code: L01FD04

Mechanism of action

Enhertu, trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate. The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a

tetrapeptide-based cleavable linker. The antibody-drug conjugate is stable in plasma. The function of the antibody portion is to bind to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. DXd, an exatecan derivative, is approximately 10 times more potent than SN-38, the active metabolite of irinotecan.

In vitro studies indicate that the antibody portion of trastuzumab deruxtecan, which has the same amino acid sequence as trastuzumab, also binds to FcγRIIIa and complement C1q. The antibody mediates antibody-dependent cellular cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2. In addition, the antibody inhibits signalling through the phosphatidylinositol 3-kinase (PI3-K) pathway in human breast cancer cells that overexpress HER2.

Clinical efficacy

The efficacy and safety of Enhertu were studied in DESTINY-Breast01, a multicentre, open-label, single-arm Phase 2 study that enrolled patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2-based regimens, including trastuzumab emtansine (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumour samples were required to show HER2 positivity defined as HER2 IHC 3+ or ISH-positive. The study excluded patients with a history of treated ILD or ILD at screening, patients with untreated or symptomatic brain metastases, and patients with a history of clinically significant cardiac disease. Patients enrolled had at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Enhertu was administered by intravenous infusion at 5.4 mg/kg once every three weeks until disease progression, death, withdrawal of consent, or unacceptable toxicity. The primary efficacy outcome measure was confirmed objective response rate (ORR) according to RECIST v1.1 in the intent-to-treat (ITT) population as evaluated by independent central review. The secondary efficacy outcome measure was duration of response (DOR).

Of the 184 patients enrolled in DESTINY-Breast01, baseline demographic and disease characteristics were: median age 55 years (range: 28 to 96); 65 years or older (23.9%); female (100%); White (54.9%), Asian (38.0%), Black or African-American (2.2%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (55.4%) or 1 (44.0%); hormone receptor status (positive: 52.7%); presence of visceral disease (91.8%); previously treated and stable brain metastases (13.0%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); sum of diameters of target lesions (< 5 cm: 42.4%, ≥ 5 cm: 50.0%).

An earlier analysis (median duration of follow-up 11.1 months [range: 0.7 to 19.9 months]) showed a confirmed objective response rate of 60.9% (95% CI: 53.4, 68.0) with 6.0% being complete responders and 54.9% being partial responders; 36.4% had stable disease, 1.6% had progressive disease and 1.1% were not evaluable. Median duration of response at that time was 14.8 months (95% CI: 13.8, 16.9) with 81.3% of responders having a response of ≥ 6 months (95% CI: 71.9, 87.8). Efficacy results from an updated data cutoff with median duration of follow-up of 20.5 months (range: 0.7 to 31.4 months) are shown in Table 4.

Table 4: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 N = 184
Confirmed objective response rate (95% CI)*†	61.4% (54.0, 68.5)
Complete response (CR)	6.5%
Partial response (PR)	54.9%
Duration of response‡	
Median, months (95% CI)	20.8 (15.0, NR)
% with duration of response ≥ 6 months (95% CI)§	81.5% (72.2, 88.0)

ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval

95% CIs calculated using Brookmeyer-Crowley method

*Confirmed responses (by blinded independent central review) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed.

†Of the 184 patients, 35.9% had stable disease, 1.6% had progressive disease and 1.1% were not evaluable.

‡Includes 73 patients with censored data

§Based on Kaplan-Meier estimation

NR = not reached

Consistent anti-tumour activity was observed across pre-specified subgroups based on prior pertuzumab therapy and hormone receptor status.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Trastuzumab deruxtecan is administered intravenously. There have been no studies performed with other routes of administration.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (V_c) of trastuzumab deruxtecan and topoisomerase I inhibitor, DXd, were estimated to be 2.77 L and 27.4 L, respectively.

In vitro, the mean human plasma protein binding of DXd was approximately 97%.

In vitro, the blood to plasma concentration ratio of DXd was approximately 0.6.

Biotransformation

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the DXd.

The humanised HER2 IgG1 monoclonal antibody is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In vitro metabolism studies in human liver microsomes indicate that DXd is metabolised mainly by CYP3A4 via oxidative pathways.

Elimination

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of DXd was 19.2 L/h. In cycle 3, the apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released DXd was approximately 7 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Following intravenous administration of DXd to rats, the major excretion pathway was faeces via the biliary route. DXd was the most abundant component in urine, faeces, and bile. Following single intravenous administration of trastuzumab deruxtecan (6.4 mg/kg) to monkeys, unchanged released DXd was the most abundant component in urine and faeces. DXd excretion was not studied in humans.

In vitro interactions

Effects of Enhertu on the pharmacokinetics of other medicinal products

In vitro studies indicate DXd does not inhibit major CYP450 enzymes including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A. *In vitro* studies indicate that DXd does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters.

Effects of other medicinal products on the pharmacokinetics of Enhertu

In vitro, DXd was a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP. No clinically meaningful interaction is expected with medicinal products that are inhibitors of MATE2-K, MRP1, P-gp, OATP1B1, or BCRP transporters (see section 4.5).

Linearity/non-linearity

The exposure of trastuzumab deruxtecan and released DXd when administered intravenously increased in proportion to dose in the 3.2 mg/kg to 8.0 mg/kg dose range (approximately 0.6 to 1.5 times the recommended dose) with low to moderate inter-subject variability. Based on population pharmacokinetic analysis, inter-subject variability in trastuzumab deruxtecan and DXd elimination clearances was approximately 25% and for central volume of distribution was approximately 16% and 42%, respectively. The intra-subject variability in trastuzumab deruxtecan and DXd AUC values (area under the serum concentration versus time curve) was approximately 8% and 14%, respectively.

Special populations

Based on population pharmacokinetic analysis, age (23-96 years), race, ethnicity, sex and body weight did not have a clinically meaningful effect on exposure of trastuzumab deruxtecan or released DXd.

Elderly

The population PK analysis showed that age (range: 23-96 years) did not affect the PK of trastuzumab deruxtecan.

Renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CL_{Cr}] \geq 60 and $<$ 90 mL/min) or moderate (CL_{Cr} \geq 30 and $<$ 60 mL/min) renal impairment (estimated by Cockcroft-Gault), the pharmacokinetics

of the released DXd was not affected by mild or moderate renal impairment as compared to normal renal function (CLcr \geq 90 mL/min).

Hepatic impairment

No dedicated hepatic impairment study was conducted. Based on population pharmacokinetic analysis, the impact of changes on pharmacokinetics of trastuzumab deruxtecan in patients with total bilirubin \leq 1.5 times ULN, irrespective of AST level, is not clinically meaningful. There are insufficient data for patients with total bilirubin $>$ 1.5 to 3 times ULN, irrespective of AST level, to draw conclusions, and no data is available for patients with total bilirubin $>$ 3 times ULN, irrespective of AST level (see sections 4.2 and 4.4).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of trastuzumab deruxtecan in children or adolescents.

5.3 Preclinical safety data

In animals, toxicities were observed in lymphatic and haematopoietic organs, intestines, kidneys, lungs, testes and skin following the administration of trastuzumab deruxtecan at exposure levels of the topoisomerase I inhibitor (DXd) below clinical plasma exposure. In these animals, antibody-drug conjugate (ADC) exposure levels were similar or above clinical plasma exposure.

DXd was clastogenic in both an *in vivo* rat bone marrow micronucleus assay and an *in vitro* Chinese hamster lung chromosome aberration assay and was not mutagenic in an *in vitro* bacterial reverse mutation assay.

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

Dedicated fertility studies have not been conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan may impair male reproductive function and fertility.

There were no animal reproductive or developmental toxicity studies conducted with trastuzumab deruxtecan. Based on results from general animal toxicity studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells (lymphatic/haematopoietic organs, intestine, or testes), and DXd was genotoxic, suggesting the potential for embryotoxicity and teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Sodium chloride solution for infusion must not be used for reconstitution or dilution since it may cause particulate formation.

6.3 Shelf life

Unopened vial

3 years.

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 °C to 8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Diluted solution

It is recommended that the diluted solution be used immediately. If not used immediately, the reconstituted solution diluted in infusion bags containing 5% glucose solution may be stored at room temperature (≤ 30 °C) for up to 4 hours or in a refrigerator at 2 °C to 8 °C for up to 24 hours, protected from light. These storage times start from the time of reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Enhertu is provided in 10 mL Type 1 amber borosilicate glass vial sealed with a fluoro-resin laminated butyl rubber stopper, and a polypropylene/aluminium yellow flip-off crimp cap. Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the following reconstitution and dilution procedures.

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted Enhertu solution required, and the number of vial(s) of Enhertu needed (see section 4.2).
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.

- If not used immediately, store the reconstituted Enhertu vials in a refrigerator at 2 °C to 8 °C for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The reconstituted product contains no preservative and is intended for single use only.

Dilution

- Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Do not use sodium chloride solution (see section 6.2). An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2 °C to 8 °C for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2 °C to 8 °C), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration, protected from light.
- Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions. Do not administer as an intravenous push or bolus (see section 4.2).
- Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1508/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 January 2021
Date of latest renewal: 12 November 2021

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Daiichi Sankyo Chemical Pharma Co., Ltd.
Onahama Plant
389-4, Izumimachi Shimokawa Aza Otsurugi, Iwaki,
Fukushima 971-8183
Japan

Name and address of the manufacturer responsible for batch release

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276 Pfaffenhofen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures are necessary for the safe and effective use of the product.

Prior to the launch in each Member State the MAH must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme with the National Competent Authority. The MAH shall ensure that in each Member State where ENHERTU (trastuzumab deruxtecan) is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and receive ENHERTU (trastuzumab deruxtecan) have access to/are provided with the following educational materials to be disseminated through professional bodies consisting of the following:

I) Healthcare Professional (HCP) Guide for ILD/pneumonitis

The HCP Guide will contain the following key elements:

- Summary of important findings of trastuzumab deruxtecan-induced ILD/pneumonitis (eg, frequency, grade, time to onset) observed in the clinical trial setting
- Description of the appropriate monitoring and evaluation of ILD/pneumonitis in patients receiving trastuzumab deruxtecan
- Detailed description of management of ILD/pneumonitis in patients treated with trastuzumab deruxtecan including guidance on drug interruption, reduction and treatment discontinuation for ILD/pneumonitis
- Reminder to HCP that they should repeat the information about signs and symptoms of ILD/pneumonitis at each patient visit, including when the patient should seek attention from an HCP (eg, the symptoms to watch for; the importance to adhere to scheduled appointments).
- Reminder to HCP to provide the patient with the Patient Card (PC), including advice that the PC should be kept with the patient at all times.

Patient Card

The Patient Card will contain the following key elements:

- Description of the important risks of ILD/pneumonitis associated with the use of trastuzumab deruxtecan
- Description of key signs and symptoms of ILD/pneumonitis and guidance on when to seek attention from an HCP
- Contact details of the trastuzumab deruxtecan prescriber
- Cross-reference to Patient Information Leaflet

II) Healthcare Professional Guide for prevention of medication errors

The HCP Guide will contain the following key elements:

- Alert to HCPs about a potential risk of confusion between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla® (trastuzumab emtansine)
- Mitigation measures for prescribing errors due to similarities in active ingredient names and measures to avoid errors during prescription phase by physicians
- Comparison of commercial appearance between Enhertu (trastuzumab deruxtecan) and other trastuzumab-containing products and the HER2-targeted antibody-drug conjugate Kadcyla® (trastuzumab emtansine).
- Potential mitigation strategies to avoid errors during preparation phase by pharmacists
- Detailed Information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase by nurses

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measure:

Description	Due date
In order to confirm the efficacy and safety of Enhertu in the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2-based regimens, the MAH should submit the interim results of study DS-8201-A-U301, a phase 3, multicentre, randomised, open-label, active-controlled study of Enhertu versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects pre-treated with prior standard of care HER2 therapies, including T-DM1.	4Q 2022

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Enhertu 100 mg powder for concentrate for solution for infusion
trastuzumab deruxtecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder for concentrate for solution for infusion contains: 100 mg of trastuzumab deruxtecan.
After reconstitution, one vial of 5 mL solution contains 20 mg/mL of trastuzumab deruxtecan

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

Enhertu should not be substituted with trastuzumab or trastuzumab emtansine.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C to 8°C).
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1508/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Enhertu 100 mg powder for concentrate for solution for infusion
trastuzumab deruxtecan
For i.v. use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

100 mg

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Enhertu 100 mg powder for concentrate for solution for infusion trastuzumab deruxtecan

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Enhertu is and what it is used for
2. What you need to know before you are given Enhertu
3. How you are given Enhertu
4. Possible side effects
5. How to store Enhertu
6. Contents of the pack and other information

1. What Enhertu is and what it is used for

What Enhertu is

Enhertu is a cancer medicine that contains the active substance trastuzumab deruxtecan. One part of the medicine is a monoclonal antibody that attaches specifically to cells that have the protein HER2 on their surface (HER2-positive), as some breast cancer cells do. The other active part of Enhertu is DXd, a substance that can kill cancer cells. Once the medicine has attached to HER2-positive cancer cells, the DXd enters the cells and kills them.

What Enhertu is used for

Enhertu is used to treat adults who have:

- **HER2-positive breast cancer** that has spread to other parts of the body or cannot be removed by surgery, and
- tried at least two other treatments specifically for HER2-positive breast cancer.

2. What you need to know before you are given Enhertu

You must not be given Enhertu

- if you are allergic to trastuzumab deruxtecan or any of the other ingredients of this medicine (listed in section 6).

If you are not sure if you are allergic, talk to your doctor or nurse before you are given Enhertu.

Warnings and precautions

Talk to your doctor or nurse before you are given Enhertu, or during treatment, if you have:

- cough, shortness of breath, fever, or other new or worsening breathing problems. These may be symptoms of a serious and potentially fatal lung disease called interstitial lung disease.
- chills, fever, sores in your mouth, stomach pain or pain when urinating. These may be symptoms of an infection caused by a reduced number of white blood cells called neutrophils.
- new or worsening shortness of breath, cough, tiredness, swelling of ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness. These may be symptoms of a condition in which your heart cannot pump blood well enough (decreased left ventricular ejection fraction).
- liver problems. Your doctor may have to monitor your liver while you are taking this medicine.

Your doctor will carry out tests before and during treatment with Enhertu.

Children and adolescents

Enhertu is not recommended for anyone under the age of 18 years. This is because there is no information on how well it works in this age group.

Other medicines and Enhertu

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding, contraception and fertility

- **Pregnancy**
Enhertu is **not recommended** during pregnancy because this medicine may harm the unborn baby.
Speak with your doctor immediately if you are pregnant, think you may be pregnant or are planning to become pregnant before or during treatment.
- **Breast-feeding**
You should not breast-feed during treatment with Enhertu and for at least 7 months after your last dose. This is because it is not known whether Enhertu passes into breast milk. Talk to your doctor about this.
- **Contraception**
Use effective contraception (birth control) to avoid becoming pregnant while being treated with Enhertu.

Women taking Enhertu should continue contraception for at least 7 months after the last dose of Enhertu.

Men taking Enhertu whose partner may become pregnant should use effective contraception:

- during treatment and
- for at least 4 months after the last dose of Enhertu.

Talk to your doctor about the best contraception for you. Also talk to your doctor before you stop your contraception.

- **Fertility**
If you are a man being treated with Enhertu, you should not father a child for 4 months after treatment and take advice on conserving sperm before treatment because the medicine may reduce your fertility. Therefore, discuss this with your doctor before starting treatment.

Driving and using machines

Enhertu is not likely to reduce your ability to drive or use machines. Be careful if you feel tired, dizzy, or have a headache.

3. How you are given Enhertu

Enhertu will be given to you in a hospital or clinic:

- The recommended dose of Enhertu is 5.4 mg for every kilogram of your weight, every 3 weeks.
- Your doctor or nurse will give you Enhertu by infusion (drip) into your vein.
- Your first infusion will be given over 90 minutes. If this goes well, the infusion on your next visits may be given over 30 minutes.
- Your doctor will decide how many treatments you need.
- If you get infusion-related symptoms, your doctor or nurse may slow down your infusion or interrupt or stop your treatment.
- Before and during treatment with Enhertu, your doctor will carry out tests that may include:
 - blood tests to check your blood cells, liver and kidneys
 - testing to check your heart and lungs.
- Your doctor may lower your dose, or temporarily or permanently stop your treatment depending on your side effects.

If you miss an appointment to get Enhertu

Contact your doctor right away to reschedule your appointment.

It is very important that you do not miss a dose of this medicine.

If you stop receiving Enhertu

Do not stop treatment with Enhertu without checking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you get any side effects, including those not listed in this leaflet.

Speak with your doctor immediately if you notice any of the following symptoms. They may be signs of a serious, possibly fatal, condition. Getting medical treatment right away may help keep these problems from becoming more serious.

Very common (may affect more than 1 in 10 people)

- A lung disease called interstitial lung disease with symptoms that can include cough, shortness of breath, fever, or other new or worsening breathing problems
- An infection caused by reduced number of neutrophils (a type of white blood cell) with symptoms that can include chills, fever, sores in your mouth, stomach pain or pain when urinating
- A heart problem called decreased left ventricular ejection fraction with symptoms that can include new or worsening shortness of breath, cough, tiredness, swelling of ankles or legs, irregular heartbeat, sudden weight gain, dizziness or unconsciousness

Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)

- nausea (feeling sick), vomiting
- constipation

- abdominal (belly) pain, indigestion
- decreased appetite
- diarrhoea
- tiredness
- hair loss, rash
- cough
- headache
- infections of the nose and throat, including flu-like symptoms
- blisters in or around your mouth
- breathing difficulties
- nosebleed
- dry eye
- dizziness
- blood tests showing low blood potassium level
- blood tests showing decreased red or white blood cells, or platelets
- blood tests showing increased levels of the liver enzymes aspartate aminotransferase or alanine aminotransferase

Common (may affect up to 1 in 10 people)

- reactions related to the infusion of the medicine which may include fever, chills, flushing, itching or rash
- fever along with a decreased number of white blood cells called neutrophils

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enhertu

Enhertu will be stored by healthcare professionals at the hospital or clinic where you receive treatment. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and vial after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C). Do not freeze.
- The prepared solution for infusion is stable for up to 24 hours at 2 °C - 8 °C protected from light and must be discarded thereafter.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Enhertu contains

- The active substance is trastuzumab deruxtecan.
One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution contains 20 mg/mL of trastuzumab deruxtecan.
- The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80.

What Enhertu looks like and contents of the pack

Enhertu is a white to yellowish-white lyophilised powder supplied in a clear amber vial with a rubber stopper, aluminium seal and plastic flip-off cap.
Each carton contains 1 vial.

Marketing Authorisation Holder

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

Manufacturer

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276 Pfaffenhofen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Daiichi Sankyo Belgium N.V.-S.A
Tél/Tel: +32-(0) 2 227 18 80

Lietuva

UAB AstraZeneca Lietuva
Tel: +370 5 2660550

България

АстраЗенека България ЕООД
Тел.: +359 24455000

Luxembourg/Luxemburg

Daiichi Sankyo Belgium N.V.-S.A
Tél/Tel: +32-(0) 2 227 18 80

Česká republika

AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

Magyarország

AstraZeneca Kft.
Tel.: +36 1 883 6500

Danmark

Daiichi Sankyo Nordics ApS
Tlf: +45 (0) 88 44 45 45

Malta

Daiichi Sankyo Europe GmbH
Tel: +49-(0) 89 7808 0

Deutschland

Daiichi Sankyo Deutschland GmbH
Tel: +49-(0) 89 7808 0

Nederland

Daiichi Sankyo Nederland B.V.
Tel: +31-(0) 20 4 07 20 72

Eesti

AstraZeneca
Tel: +372 6549 600

Norge

Daiichi Sankyo Nordics ApS
Tlf: +47 (0) 21 09 38 29

Ελλάδα

AstraZeneca A.E.
Τηλ: +30 210 6871500

Österreich

Daiichi Sankyo Austria GmbH
Tel: +43 (0) 1 485 86 42 0

España

Daiichi Sankyo España, S.A.
Tel: +34 91 539 99 11

Polska

AstraZeneca Pharma Poland Sp. z o.o.
Tel: +48 22 245 73 00

France

Daiichi Sankyo France S.A.S.
Tél: +33 (0) 1 55 62 14 60

Portugal

Daiichi Sankyo Portugal, Unip. LDA
Tel: +351 21 4232010

Hrvatska

AstraZeneca d.o.o.
Tel: +385 1 4628 000

Ireland

Daiichi Sankyo Ireland Ltd
Tel: +353-(0) 1 489 3000

Ísland

Daiichi Sankyo Nordics ApS
Sími: +45 (0) 88 44 45 45

Italia

Daiichi Sankyo Italia S.p.A.
Tel: +39-06 85 2551

Κύπρος

Αλέκτωρ Φαρμακευτική Λτδ
Τηλ: +357 22490305

Latvija

SIA AstraZeneca Latvija
Tel: +371 67377100

România

AstraZeneca Pharma SRL
Tel: +40 21 317 60 41

Slovenija

AstraZeneca UK Limited
Tel: +386 1 51 35 600

Slovenská republika

AstraZeneca AB, o.z.
Tel: +421 2 5737 7777

Suomi/Finland

Daiichi Sankyo Nordics ApS
Puh/Tel: +358 (0) 9 3540 7081

Sverige

Daiichi Sankyo Nordics ApS
Tel: +46 (0) 40 699 2524

United Kingdom (Northern Ireland)

Daiichi Sankyo Europe GmbH
Tel: +49 (0) 89 7808 0

This leaflet was last revised in {MM/YYYY}

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

In order to prevent medicinal product errors, check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.

Appropriate procedures for the preparation of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the following reconstitution and dilution procedures

Reconstitution

- Reconstitute immediately before dilution.
- More than one vial may be needed for a full dose. Calculate the dose (mg), the total volume of reconstituted Enhertu solution required, and the number of vial(s) of Enhertu needed.
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of water for injection into each vial to obtain a final concentration of 20 mg/mL.
- Swirl the vial gently until completely dissolved. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The solution should be clear and colourless to light yellow. Do not use if visible particles are observed or if the solution is cloudy or discoloured.

- If not used immediately, store the reconstituted Enhertu vials in a refrigerator at 2 °C to 8 °C for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- The reconstituted product contains no preservative and is intended for single use only.

Dilution

- Dilute the calculated volume of reconstituted Enhertu in an infusion bag containing 100 mL of 5% glucose solution. Do not use sodium chloride solution. An infusion bag made of polyvinylchloride or polyolefin (copolymer of ethylene and polypropylene) is recommended.
- Gently invert the infusion bag to thoroughly mix the solution. Do not shake.
- Cover the infusion bag to protect from light.
- If not used immediately, store at room temperature for up to 4 hours including preparation and infusion or in a refrigerator at 2 °C to 8 °C for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

Administration

- If the prepared infusion solution was stored refrigerated (2 °C to 8 °C), it is recommended that the solution be allowed to equilibrate to room temperature prior to administration, protected from light.
- Administer Enhertu as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter.
- The initial dose should be administered as a 90-minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of Enhertu may be administered as 30-minute infusions. Do not administer as an intravenous push or bolus.
- Do not mix Enhertu with other medicinal products or administer other medicinal products through the same intravenous line.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.