

▼ 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 one 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 5.0 (NCI-CTCAE v.5.0).

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 [CLcr] ≥ 60 and < 90 mL/min) or moderate (CLcr ≥ 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/pneumonitis leading to an increase in discontinuation of therapy has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully for adverse reactions including ILD/pneumonitis (see section 4.4).

Hepatic impairment

No dose adjustment is required in patients with total bilirubin \leq 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., \geq 0.5 mg/kg/day 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. \geq 1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Enhertu should be permanently discontinued in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD/pneumonitis (see section 4.2). Patients with a history of ILD/pneumonitis or patients with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis and should be monitored carefully (see section 4.2).

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. 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. LVEF decrease should be managed through treatment interruption. 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 pooled safety population has been evaluated for patients who received at least one dose of Enhertu 5.4 mg/kg (n = 573) across multiple tumour types in clinical studies. The median duration of treatment in this pool was 11.3 months (range: 0.7 to 37.9 months).

The most common adverse reactions were nausea (77.0%), fatigue (57.2%), vomiting (46.8%), alopecia (38.0%), neutropenia (34.6%), constipation (33.9%), decreased appetite (33.7%), anaemia (32.3%), diarrhoea (30.7%), musculoskeletal pain (27.4%), transaminases increased (24.4%), leukopenia (24.1%), thrombocytopenia (23.0%), and upper respiratory tract infection (22.7%).

The most common National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0) Grade 3 or 4 adverse reactions were neutropenia (17.5%), anaemia (8.4%), fatigue (6.3%), nausea (6.3%), leukopenia (5.9%), thrombocytopenia (5.8%), lymphopenia (4.4%), hypokalaemia (4.0%), transaminases increased (2.8%), vomiting (2.6%), diarrhoea (2.1%), pneumonia

(1.4%), febrile neutropenia (1.4%), and decreased appetite (1.2%). Grade 5 adverse reactions occurred in 1.6% of patients, including ILD (1.4%).

Dose interruptions due to adverse reactions occurred in 33.9% of patients treated with Enhertu. The most frequent adverse reactions associated with dose interruption were neutropenia (14.0%), fatigue (3.8%), leukopenia (3.7%), thrombocytopenia (3.3%), anaemia (3.3%), upper respiratory tract infection (3.0%), nausea (2.6%), ILD (2.4%), and pneumonia (2.3%). Dose reductions occurred in 18.8% of patients treated with Enhertu. The most frequent adverse reactions associated with dose reduction were nausea (4.9%), fatigue (3.7%), and neutropenia (3.0%). Discontinuation of therapy due to an adverse reaction occurred in 11.9% of patients treated with Enhertu. The most frequent adverse reaction associated with permanent discontinuation was ILD (8.6%).

Tabulated list of adverse reactions

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 5.4 mg/kg in multiple tumour types

System organ class/preferred term or grouped term	Frequency
Infections and infestations	
Upper respiratory tract infection ^a	Very common
Pneumonia	Common
Blood and lymphatic system disorders	
Neutropenia ^b	Very common
Anaemia ^c	Very common
Leukopenia ^d	Very common
Thrombocytopenia ^e	Very common
Lymphopenia ^f	Very common
Febrile neutropenia	Common
Metabolism and nutrition disorders	
Hypokalaemia ^g	Very common
Decreased appetite	Very common
Dehydration	Common
Nervous system disorders	
Headache ^h	Very common
Dizziness	Very common
Dysgeusia	Common
Eye disorders	
Vision blurred	Common

System organ class/preferred term or grouped term	Frequency
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease ⁱ	Very common
Dyspnoea	Very common
Cough	Very common
Epistaxis	Very common
Gastrointestinal disorders	
Nausea	Very common
Vomiting	Very common
Diarrhoea	Very common
Abdominal pain ^j	Very common
Constipation	Very common
Stomatitis ^k	Very common
Dyspepsia	Very common
Hepatobiliary disorders	
Transaminases increased ^l	Very common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Rash ^m	Common
Skin hyperpigmentation ⁿ	Common
Pruritus	Common
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain ^o	Very common
General disorders and administration site conditions	
Fatigue ^p	Very common
Pyrexia	Very common
Oedema peripheral	Common
Investigations	
Ejection fraction decreased ^q	Very common
Weight decreased	Very common
Blood alkaline phosphatase increased	Common
Blood bilirubin increased ^r	Common
Blood creatinine increased	Common
Injury, poisoning and procedural complications	
Infusion-related reactions ^s	Common

^a Includes influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, rhinitis, 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 thrombocytopenia and platelet count decreased.
- ^f Includes lymphopenia and lymphocyte count decreased.
- ^g Includes hypokalaemia and blood potassium decreased.
- ^h Includes headache, sinus headache, and migraine.
- ⁱ Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis (n = 34), interstitial lung disease (n = 24), organising pneumonia (n = 4), pneumonia (n = 1), pulmonary mass (n = 1), acute respiratory failure (n = 1), lung infiltration (n = 1), lymphangitis (n = 1), pulmonary fibrosis (n = 1), respiratory failure (n = 4), and alveolitis (n = 2).
- ^j Includes abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.
- ^k Includes stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, and oral mucosal eruption.
- ^l Includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.
- ^m Includes rash, rash pustular, and rash maculopapular.
- ⁿ Includes skin hyperpigmentation, skin discolouration, and pigmentation disorder.
- ^o Includes back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.
- ^p Includes asthenia, fatigue, malaise, and lethargy.
- ^q Includes laboratory parameters of LVEF decrease (n = 86) and/or preferred terms of ejection fraction decreased (n = 12), cardiac failure (n = 1), cardiac failure congestive (n = 1), and left ventricular dysfunction (n = 1).
- ^r Includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
- ^s Cases of infusion-related reactions include infusion-related reaction (n = 11), hypersensitivity (n = 2), and flushing (n = 1).

Description of selected adverse reactions

Interstitial lung disease/pneumonitis

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 573), ILD occurred in 12.0% of patients. Most ILD cases were Grade 1 (2.6%) and Grade 2 (7.3%). Grade 3 cases occurred in 0.7% and no Grade 4 cases occurred. Grade 5 events occurred in 1.4% of patients. Median time to first onset was 5.5 months (range: 1.1 to 20.8) (see sections 4.2 and 4.4).

In patients treated with Enhertu 6.4 mg/kg in clinical studies across multiple tumour types (n = 619), ILD occurred in 16.6% of patients. Most ILD cases were Grade 1 (4.7%) and Grade 2 (8.4%). Grade 3 cases occurred in 1.5% and Grade 4 cases occurred in 0.2% of patients. Grade 5 events occurred in 1.9% of patients. One patient had pre-existing ILD that worsened post treatment leading to Grade 5 ILD. Median time to first onset was 4.2 months (range: -0.5 to 21.0).

Neutropenia

In patients treated with Enhertu 5.4 mg/kg in clinical studies (n = 573) across multiple tumour types, neutropenia was reported in 34.6% of patients and 17.5% had Grade 3 or 4 events. Median time of onset was 54 days (range: 1 day 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 1.4% of patients (see section 4.2).

Left ventricular ejection fraction decrease

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 573), LVEF decrease was reported in 15 patients (2.6%), of which 2 (0.3%) were Grade 1, 11 (1.9%) were Grade 2, and 2 (0.3%) were Grade 3. The observed frequency of LVEF decreased based on laboratory parameters (echocardiogram or MUGA scanning) was 85/539 (15.8%) for Grade 2, and 1 (0.2%) for Grade 3. Treatment with Enhertu has not been studied in patients with LVEF less than 50% prior to initiation of treatment (see section 4.2).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Across all doses evaluated in clinical studies, 2.1% (27/1311) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with Enhertu. The incidence of neutralising antibodies against trastuzumab deruxtecan was 0.1% (1/1311). There was no association between development of antibodies and allergic-type reactions.

Paediatric population

Safety has not been established in this population.

Elderly

In patients treated with Enhertu 5.4 mg/kg in clinical studies across multiple tumour types (n = 573), 25.0% were 65 years or older and 4.2% were 75 years or older. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (51.7%) as compared to patients younger than 65 years old (41.4%), leading to more discontinuations due to adverse reactions.

To report any side effect(s):

- **Saudi Arabia:**

- The National Pharmacovigilance Centre (NPC)
 - Fax: +966-11-205-7662
 - Toll free phone: 19999
 - E-mail: npc.drug@sfd.gov.sa
 - Website: <https://ade.sfd.gov.sa/>

- Other GCC States:

- Please contact the relevant competent authority.

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

DESTINY-Breast03

The efficacy and safety of Enhertu were studied in DESTINY-Breast03, a multicentre, open-label, active-controlled, randomised, two-arm phase 3 study that enrolled patients with HER2-positive, unresectable or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

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 ILD/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening, patients with untreated or symptomatic brain metastases, patients with a history of clinically significant cardiac disease, and patients with prior treatment with an anti-HER2 antibody-drug conjugate in the metastatic setting. Patients were randomised 1:1 to receive either Enhertu 5.4 mg/kg (N = 261) or trastuzumab emtansine 3.6 mg/kg (N = 263) administered by intravenous infusion once every three weeks. Randomisation was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression-free survival (PFS) as evaluated by blinded independent central review (BICR) according to RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure. PFS based on investigator assessment, confirmed objective response rate (ORR), duration of response (DOR), patient-reported outcomes (PRO), and time to hospitalisation were secondary endpoints.

Patient demographics and baseline disease characteristics were balanced between treatment arms. Of the 524 patients randomised, the baseline demographic and disease characteristics were: median age 54 years (range: 20 to 83); 65 years or older (20.2%); female (99.6%); Asian (59.9%), White (27.3%), Black or African American (3.6%); Eastern Cooperative Oncology Group (ECOG) performance status 0 (62.8%) or 1 (36.8%); hormone receptor status (positive: 51.9%); presence of visceral disease (73.3%); previously treated and stable brain metastases (21.8%); and 48.3% of patients received one line of prior systemic therapy in the metastatic setting. The percentage of patients who had not received prior treatment for metastatic disease was 9.5%. The percentage of patients who were previously treated with pertuzumab was 61.1%.

At the prespecified interim analysis for PFS based on 245 events (73% of total events planned for final analysis), the study demonstrated a statistically significant improvement in PFS per BICR in patients randomized to Enhertu compared to trastuzumab emtansine. Overall survival (OS) was immature at the time of analysis.

Table 4: Efficacy results in DESTINY-Breast03 (intent-to-treat analysis set)

Efficacy Parameter	Enhertu N = 261	trastuzumab emtansine N = 263
Progression-free survival (PFS) primary endpoint (BICR)		
Number of events (%)	87 (33.3)	158 (60.1)
Median, months (95% CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95% CI)	0.28 (0.22, 0.37)	
p-value	p < 0.000001 [†]	
Overall survival (OS) key secondary endpoint		
Number of events (%)	33 (12.6)	53 (20.2)
Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)
Survival at 9 months (95% CI)	96.1% (92.8, 97.9)	91.3% (87.1, 94.2)
Hazard ratio (95% CI)	0.55 (0.36, 0.86)	
PFS per investigator assessment		
Number of events (%)	78 (29.9)	168 (63.9)
Median, months (95% CI)	25.1 (22.1, NE)	7.2 (6.8, 8.3)
Hazard ratio (95% CI)	0.26 (0.20, 0.35)	
Confirmed objective response rate (ORR) per BICR		
n (%)	208 (79.7)	90 (34.2)
95% CI	(74.3, 84.4)	(28.5, 40.3)
Complete response n (%)	42 (16.1)	23 (8.7)
Partial response n (%)	166 (63.6)	67 (25.5)
Duration of response per BICR		
Median, months (95% CI)	NR (20.3, NE)	NR (12.6, NE)

CI = confidence interval; NE = not estimable; NR = not reached

[†]presented as 6 decimal places

Figure 1: Kaplan-Meier plot of progression-free survival per BICR (intent-to-treat analysis set)

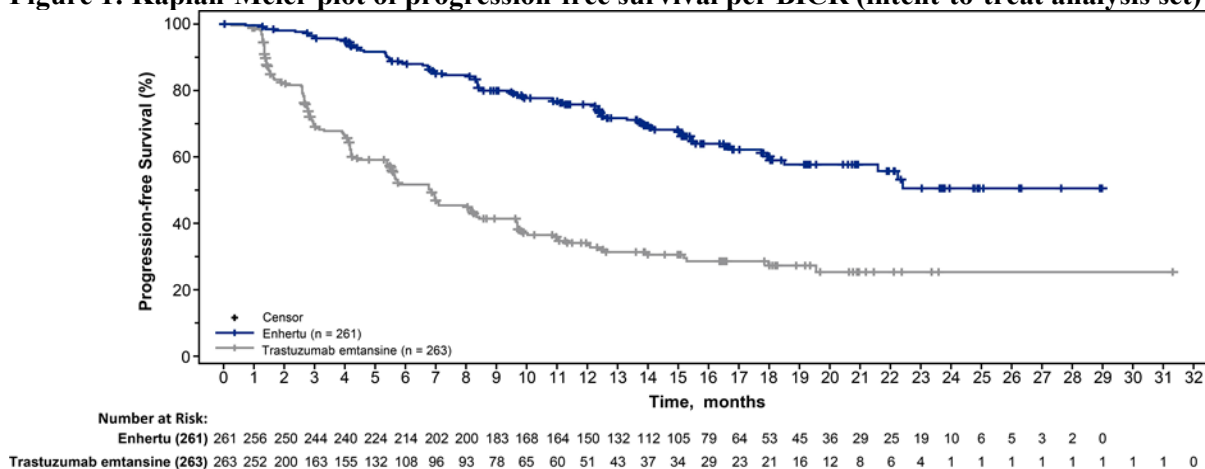
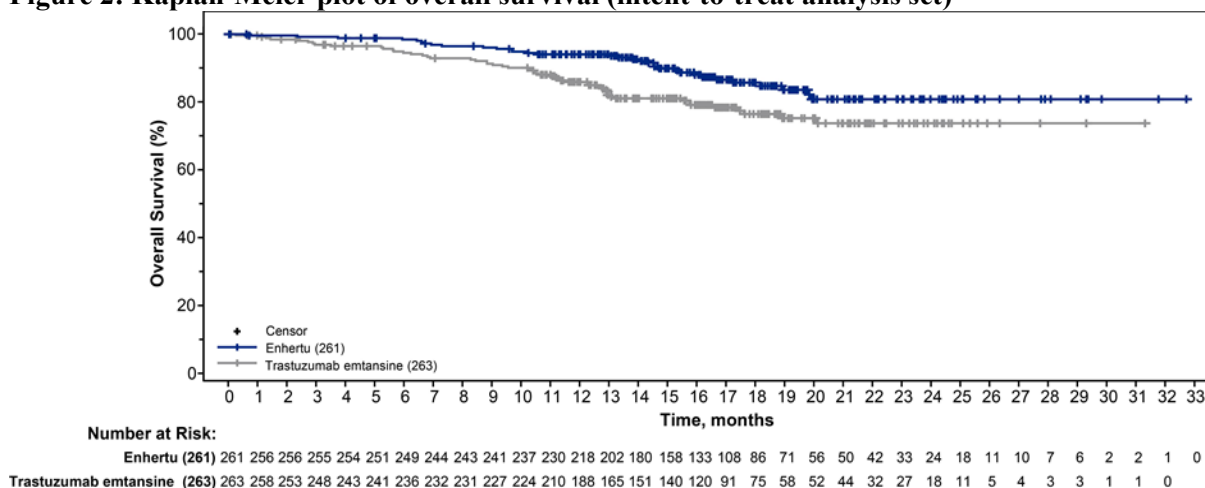


Figure 2: Kaplan-Meier plot of overall survival (intent-to-treat analysis set)



Similar PFS results were observed across prespecified subgroups including prior pertuzumab therapy, hormone receptor status, and presence of visceral disease.

DESTINY-Breast01

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 5.

Table 5: 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 prespecified 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 2.71 L and 27.0 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 19.4 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 (20-96 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: 20-96 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}] ≥ 60 and <90 mL/min) or moderate (CL_{cr} ≥ 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 (CL_{Cr} ≥ 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 ≤ 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 4.45 mg
L-histidine hydrochloride monohydrate 20.2 mg
Sucrose 450 mg
Polysorbate 80 (1.50 mg)

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

4 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).
- Cover the infusion bag to protect from light.
- 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

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8. MANUFACTURER

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9. DATE OF REVISION OF THE TEXT

09 June 2022.