

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ENHERTU[®] (trastuzumab deruxtecan) powder for injection

1 NAME OF THE MEDICINE

Trastuzumab deruxtecan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of lyophilized powder for concentrate for solution for infusion delivers 100 mg of trastuzumab deruxtecan. After reconstitution, one vial of 5 mL solution delivers 20 mg/mL of trastuzumab deruxtecan (see Section 4.2 Dose and method of administration).

For the full list of excipients, see Section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Powder for injection.

White to yellowish-white lyophilized powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENHERTU 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.

This indication is approved via the **provisional approval** pathway, based on overall response rate and duration of response. Full registration for this indication depends on verification and description of clinical benefit in a confirmatory trial.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do not substitute ENHERTU for or with trastuzumab or trastuzumab emtansine. 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.

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 initial infusion is well tolerated, subsequent doses of ENHERTU may be administered as 30-minute infusions.

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.

Antiemetics may be administered in accordance with local medical practice as per patient tolerance for prophylaxis or management.

Dose Modifications

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU per guidelines provided in Table 1 and Table 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 Special warnings and precautions for use/<i>Interstitial lung disease/pneumonitis</i>).
	Symptomatic ILD/Pneumonitis (Grade 2 or greater)	<ul style="list-style-type: none"> Permanently discontinue ENHERTU.

Adverse Reaction	Severity		Treatment Modification
			<ul style="list-style-type: none"> Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/<i>Interstitial lung disease/pneumonitis</i>).
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 $1 \times 10^9/L$ and temperature greater than $38.3^\circ C$ or a sustained temperature of $38^\circ C$ 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).
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.

Adverse Reaction	Severity	Treatment Modification
		<ul style="list-style-type: none"> 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 patient populations

Use in the elderly

No dose adjustment of ENHERTU is required in patients aged 65 years or older.

Paediatric use

The safety and efficacy in children and adolescents below 18 years of age have not been established as there is no relevant use in the paediatric population for the indication of metastatic breast cancer.

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. No data are available in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin \leq ULN and any AST $>$ ULN or total bilirubin > 1 to 1.5 times ULN and any AST) hepatic impairment. There are insufficient data to make a recommendation on dose adjustment in patients with moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. No data are available in patients with severe (total bilirubin > 3 to 10 times ULN and any AST) hepatic impairment.

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.

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.
- Reconstitute each 100 mg vial using a sterile syringe to slowly inject 5 mL of sterile 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 discoloration. 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 product does not contain a preservative. Discard unused ENHERTU after 24 hours refrigerated.

Dilution

Calculation to determine the volume of reconstituted ENHERTU (mL) to be further diluted:

$$\text{Reconstituted ENHERTU (mL)} = \frac{\text{ENHERTU dose (mg/kg)} \times \text{Patient's Body Weight (kg)}}{20 \text{ mg/mL}}$$

- Dilute the calculated volume of reconstituted ENHERTU in an infusion bag containing 100 mL of 5% dextrose solution. Do not use sodium chloride solution (see Section 6.2 Incompatibilities). 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.
- Administer ENHERTU as an intravenous infusion only with a 0.20 or 0.22 micron in-line polyethersulfone (PES) or polysulfone (PS) filter. 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.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial Lung Disease/Pneumonitis

Cases of interstitial lung disease (ILD) and/or pneumonitis, have been reported with ENHERTU [see Section 4.8 Adverse effects (undesirable effects)]. Fatal outcomes have been observed. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 13.7% of patients as determined by independent review. Most ILD cases were Grade 1 (2.6%), Grade 2 (8.1%), or Grade 3 (0.4%). Grade 5 events occurred in 2.6% of patients. Median time to first onset was 4.4 months (range: 1.2 to 11.1).

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. Consultation with a pulmonologist should be considered. For asymptomatic (Grade 1) ILD/pneumonitis, consider corticosteroid treatment (e.g., ≥ 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 systemic corticosteroid treatment (e.g., ≥ 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 Dose and method of administration). 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. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 32.5% of patients and 18.8% had Grade 3 or 4 events. Febrile neutropenia was reported in 1.7% of patients.

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 Dose and method of administration).

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 were reported. No decreases of LVEF to less than 40% were observed. Treatment with ENHERTU has not been studied in patients with LVEF less than 50% prior to initiation of treatment.

LVEF should be assessed 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 Dose and method of administration).

Embryo Fetal Toxicity

ENHERTU can cause fetal 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 can also cause embryo-fetal harm when administered to a pregnant woman (see Section 4.6 Fertility, pregnancy and lactation).

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 fetus. 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 Fertility, pregnancy and lactation).

Use in the elderly

Please see Section 4.2 Dose and method of administration/ *Use in the elderly*

Paediatric use

Please see Section 4.2 Dose and method of administration/ *Paediatric use*

Effects on laboratory tests

Please see Section 4.8 Adverse effects (Undesirable effects)/ *Laboratory Abnormalities (Table 4)*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of Other Medicinal Products on the Pharmacokinetics of ENHERTU

In vitro studies indicate that the released topoisomerase I inhibitor is a substrate of the following transporters: P-glycoprotein (P-gp), OATP1B1, OATP1B3, MATE2K, MRP1, and BCRP. Inhibitors of these transporters could increase plasma concentrations of the released topoisomerase I inhibitor.

Coadministration of ritonavir (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a dual inhibitor of OATP1B/CYP3A, increased exposure (AUC) of trastuzumab deruxtecan by 19% and the released topoisomerase I inhibitor by 22%.

Coadministration of itraconazole (200 mg twice daily from day 17 of cycle 2 to day 21 of cycle 3), a strong CYP3A inhibitor, increased exposure (AUC) of trastuzumab deruxtecan by 11% and the released topoisomerase I inhibitor by 18%.

Coadministration with ritonavir, a dual inhibitor of OATP1B/CYP3A, or with itraconazole, a strong CYP3A inhibitor, resulted in no clinically meaningful increase in exposures of trastuzumab deruxtecan or the released topoisomerase I inhibitor. No dose adjustment is required during coadministration of trastuzumab deruxtecan with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P-gp, MATE2-K, MRP1, or BCRP transporters.

Effects of ENHERTU on the Pharmacokinetics of Other Medicinal Products

In vitro studies indicate that the topoisomerase I inhibitor does not inhibit or induce major CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A. *In vitro* studies indicate that the topoisomerase I inhibitor does not inhibit OAT3, OCT1, OCT2, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, or BSEP transporters, but has an inhibitory effect on OAT1 and OATP1B1 with IC₅₀ values of 12.7 and 14.4 µmol/L, respectively, which are significantly higher than steady-state C_{max} (0.01 µmol/L) of topoisomerase I inhibitor at 5.4 mg/kg dose administered every 3 weeks. No clinically meaningful drug-drug interaction is expected with drugs that are substrates of OAT1 or OATP1B1 transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of Childbearing Potential

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

Effects on fertility

No dedicated fertility studies have been conducted with trastuzumab deruxtecan. Repeat-dose toxicity studies with trastuzumab deruxtecan (intravenous dosing once every 3 weeks) revealed adverse changes to the male reproductive organs in rats and monkeys. In rats, treatment resulted in decreased testes and epididymides weights and spermatid retention at ≥20 mg/kg (3.3× the clinical AUC at the maximum recommended clinical dose for trastuzumab deruxtecan and 0.14× for the topoisomerase inhibitor) and tubular degeneration in testes and aspermia at 197 mg/kg (22× the clinical AUC for trastuzumab deruxtecan and 1.3× for the topoisomerase inhibitor). In monkeys, decreased spermatids in seminiferous tubules in the testes were noted at 30 mg/kg (6.5× the clinical AUC for trastuzumab deruxtecan 0.44× for the topoisomerase inhibitor). These changes in the testes of monkeys showed reversibility. 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.

Contraception in Males and Females

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.

Use in pregnancy – Category D

Trastuzumab deruxtecan can cause fetal harm when administered to a pregnant woman. There are no available data on the effects of trastuzumab deruxtecan in pregnant women. However, 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 trastuzumab deruxtecan can also cause embryo-fetal harm when administered to a pregnant woman.

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

Administration of ENHERTU to pregnant women is not recommended, and patients should be informed of the potential risks to the fetus 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.

Use in lactation

It is not known if trastuzumab deruxtecan is excreted in human milk. Since many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should discontinue breastfeeding prior to initiating treatment with ENHERTU. Women may begin breastfeeding 7 months after concluding treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENHERTU is not expected to affect patients' ability to drive or use machines. Due to potential adverse reactions such as fatigue, headache and dizziness [see Section 4.8 Adverse effects (undesirable effects)], patients should be advised to use caution when driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Breast Cancer

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 DESTINY Breast01 and Study DS8201-A-J101. Table 3 lists adverse drug reactions, with incidences regardless of investigators assessment of causality, reported in this patient population. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 9.8 months (range: 0.7 to 37.1).

In ENHERTU treated patients (n=234), the median age was 56 years (range 28 to 96); 99.6% were female; 50.9% were White, 41.5% were Asian, 3.0% were Black or African American; and 57.7% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 41.9% had an ECOG performance status of 1. The studies excluded patients with a history of treated ILD or ILD at screening and patients with a history of clinically significant cardiac disease.

The most common adverse reactions (frequency $\geq 20\%$) were nausea, fatigue, vomiting alopecia, constipation, decreased appetite, anaemia, neutropenia, diarrhoea, thrombocytopenia, cough, leukopenia, and headache (see Table 3). The most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03) Grade ≥ 3 adverse reactions (frequency $>1\%$) were neutropenia, anaemia, nausea, fatigue, leukopenia, lymphopenia, vomiting, thrombocytopenia, hypokalaemia, ILD, diarrhoea, febrile neutropenia, dyspnoea, abdominal pain, decreased appetite, and alanine aminotransferase increased (see Table 3). In six patients (2.6%) ILD led to death.

Dose interruptions due to adverse reactions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) 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 ($>2\%$) 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 11% of patients treated with ENHERTU. The most frequent adverse reaction ($>2\%$) associated with permanent discontinuation was ILD (9.4%).

Table 3: Adverse Drug Reactions Reported in DESTINY-Breast01 and DS8201-A-J101 Trials (occurred in $\geq 10\%$ of subjects for All Grades or $\geq 2\%$ for Grades 3 or 4)

System Organ Class ^a	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Gastrointestinal Disorders		
Nausea	187 (79.9)	16 (6.8)
Vomiting	114 (48.7)	10 (4.3)
Constipation	84 (35.9)	2 (0.9)

System Organ Class ^a	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Diarrhoea	72 (30.8)	6 (2.6)
Abdominal Pain ^b	46 (19.7)	3 (1.3)
Stomatitis ^c	35 (15.0)	2 (0.9)
Dyspepsia	33 (14.1)	0
General Disorders and Administration Site Conditions		
Fatigue ^d	141 (60.3)	15 (6.4)
Skin and Subcutaneous Tissue Disorders		
Alopecia	108 (46.2)	1 (0.4)
Rash ^e	30 (12.8)	1 (0.4)
Metabolism and Nutrition Disorders		
Decreased appetite	81 (34.6)	3 (1.3)
Hypokalaemia	30 (12.8)	8 (3.4)
Blood and Lymphatic System Disorders		
Anaemia ^f	79 (33.8)	21 (9.0)
Neutropenia ^g	76 (32.5)	44 (18.8)
Thrombocytopenia ^h	54 (23.1)	10 (4.3)
Leukopenia ⁱ	48 (20.5)	13 (5.6)
Lymphopenia ^j	26 (11.1)	12 (5.1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	50 (21.4)	0
Dyspnoea	34 (14.5)	4 (1.7)
Epistaxis	33 (14.1)	0
Interstitial lung disease ^k	32 (13.7)	1 (0.4)
Nervous System Disorders		
Headache ^l	47 (20.1)	0
Dizziness	25 (10.7)	0

System Organ Class ^a	ENHERTU 5.4 mg/kg N=234	
	All Grades n (%)	Grades 3 or 4 n (%)
Infections and infestations		
Upper respiratory tract infections ^k	43 (18.4)	15 (6.4)
Investigations		
Aspartate aminotransferase increased	35 (15.0)	2 (0.9)
Alanine aminotransferase increased	25 (10.7)	3 (1.3)
Eye disorders		
Dry eye	27 (11.5)	1 (0.4)

N=number of patients exposed; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

^a Based on MedDRA version 20.1

^b Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

^c Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

^d Grouped term of fatigue includes PTs of fatigue and asthenia.

^e Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

^f Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased.

^g Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.

^h Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.

ⁱ Grouped term of leukopenia includes PTs of leukopenia and white blood cell count decreased.

^j Grouped term of lymphopenia includes PTs of lymphopenia and lymphocyte count decreased.

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

^l Grouped term of headache includes PTs of headache, sinus headache, and migraine.

^k Upper respiratory tract infection (grouped term) includes PTs of upper respiratory tract infection, influenza, and influenza-like illness.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast01 and DS8201-A-J101 Trials

Laboratory Abnormalities ^a	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Haematology		
White blood cell count decreased	168 (72.4)	20 (8.6)
Anaemia	166 (71.6)	19 (8.2)
Neutrophil count decreased	150 (64.9)	41 (17.7)
Platelet count decreased	99 (42.9)	9 (3.9)
Chemistry		
Aspartate aminotransferase increased	103 (44.4)	2 (0.9)
Alanine aminotransferase increased	95 (40.9)	1 (0.4)
Hypokalaemia	64 (27.8)	9 (3.9)

^a Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 based on laboratory measurements.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose with trastuzumab deruxtecan. In the event of overdose, patients should be monitored, and appropriate supportive care should be given.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanized anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor bound by a tetrapeptide-based cleavable linker. The ADC is stable in plasma under in vitro conditions. Following binding to HER2 on tumour cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death. The topoisomerase I inhibitor, an exatecan derivative, is approximately 10 times more potent than SN38, the active metabolite of irinotecan.

Pharmacodynamic Effects

The administration of multiple doses of trastuzumab deruxtecan (6.4 mg/kg every 3 weeks) did not show any clinically meaningful effect on the QTc interval in an open-label, single-arm study in 51 patients with HER2-expressing metastatic breast cancer.

Clinical trials

Metastatic Breast Cancer

The efficacy and safety of ENHERTU were demonstrated in a Phase 2, single-agent, open-label, multicentre study: DESTINY-Breast01.

The study included adult patients with unresectable or metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 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 and patients with a history of clinically significant cardiac disease. 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 Response Evaluation Criteria in Solid Tumours (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Duration of response (DOR) and progression-free survival (PFS) were additional outcome measures.

DESTINY-Breast01 (N = 184) baseline demographic and disease characteristics were: median age 55 years (range 28 to 96); 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%); median number of prior therapies in the metastatic setting: 5 (range: 2 to 17); prior pertuzumab therapy (65.8%); sum of diameters of target lesions (<5 cm: 42.4%, ≥ 5 cm: 50.0%).

Efficacy results based on a data cut-off of 26 Mar 2021 with a median duration of follow-up of 26.5 months and median duration of treatment of 10.1 months are summarized in Table 5.

Table 5: Efficacy results in DESTINY-Breast01 (intent-to-treat analysis set)

	DESTINY-Breast01 N=184
Confirmed objective response rate (ORR) (95% CI)^{#§}	62% (54.5, 69.0)
Complete response (CR)	7.1%
Partial response (PR)	54.9%
Duration of Response (DoR)[*]	
Median, months (95% CI)	18.2 (15.0, NR)
% with duration of response \geq 6 months (95% CI) [†]	81.8% (72.5, 88.1)

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, 35.3% had stable disease, 1.6% had progressive disease and 1.1% were not evaluable.

^{*}Includes 69 patients with censored data

[†]Based on Kaplan-Meier estimates

Efficacy data based on DCO 21 March 2021, median duration of follow-up of 26.5 months

Consistent antitumor activity was observed with ENHERTU regardless of prior pertuzumab therapy and hormone receptor status. In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 66% (95% CI: 57, 75), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 57% (95% CI: 43, 69). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 60% (95% CI: 49, 70), and those who were hormone receptor negative at baseline had a confirmed ORR of 68% (95% CI: 56, 77).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. At the recommended dosage of ENHERTU, the geometric mean (coefficient of variation [CV]%) C_{max} of trastuzumab deruxtecan and DXd were 122 µg/mL (20%) and 4.4 ng/mL (40%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 735 µg·day/mL (31%) and 28 ng·day/mL (38%), respectively, based on population pharmacokinetic analysis.

Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (V_c) of trastuzumab deruxtecan was estimated to be 2.77 L.

In vitro, the mean human plasma protein binding of the topoisomerase I inhibitor was approximately 97%.

In vitro, the blood to plasma concentration ratio of the topoisomerase I inhibitor was approximately 0.6.

Metabolism

Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release the active topoisomerase I inhibitor.

The humanized 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 the topoisomerase I inhibitor is metabolized mainly by CYP3A4 via oxidative pathways.

Excretion

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 the topoisomerase I inhibitor was 19.2 L/h. The apparent elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan and released topoisomerase I inhibitor was approximately 5.7 days. Moderate accumulation (approximately 35% in cycle 3 compared to cycle 1) of trastuzumab deruxtecan was observed.

Following intravenous administration of the topoisomerase I inhibitor to rats, the major excretion pathway was faeces via the biliary route. The topoisomerase I inhibitor 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 topoisomerase I inhibitor was the most abundant component in urine and faeces.

Linearity/Nonlinearity

The exposure of trastuzumab deruxtecan and released topoisomerase I inhibitor 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 interindividual variability.

Specific populations

Age, race, ethnicity, sex and body weight

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 topoisomerase I inhibitor.

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 topoisomerase I inhibitor was not affected by mild to 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, higher levels of AST and total bilirubin resulted in a lower clearance of topoisomerase I inhibitor. The impact of these changes is not expected to be clinically meaningful.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The topoisomerase I inhibitor component of trastuzumab deruxtecan 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

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted Solution

It is recommended that the reconstituted solution be used immediately. If not used immediately, the reconstituted solution may be stored in a refrigerator at 2°C to 8°C for up to 24 hours from the time of reconstitution, protected from light.

Diluted Solution

It is recommended that the diluted solution be used immediately. If not used immediately, the diluted solution may be stored at room temperature 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 vials in a refrigerator (2°C to 8°C) until time of reconstitution.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 Shelf life.

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 glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of three components: 1) a humanized anti-HER2 IgG1 monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab, covalently linked to 2) a topoisomerase I inhibitor, an exatecan derivative, via 3) a tetrapeptide-based cleavable linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology and the topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

General structure

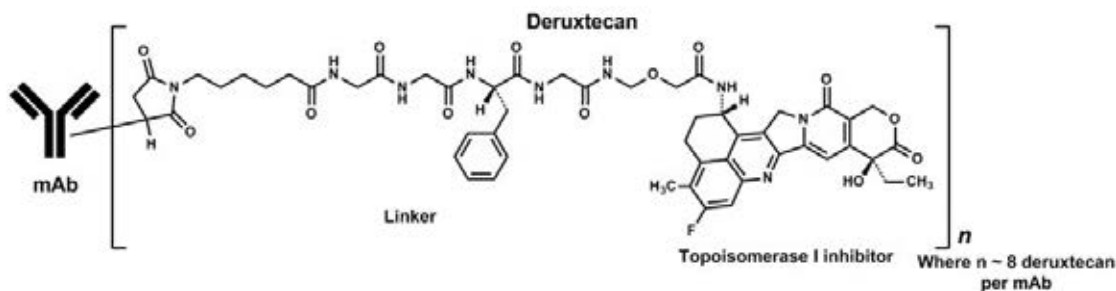


Figure 1 General structure of trastuzumab deruxtecan

CAS number

1826843-81-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

DD MMM YYYY

10 DATE OF REVISION

Not applicable.

Attachment 1 AusPAR - Enhertu – Trastuzumab deruxtecan - AstraZeneca Pty Ltd PM-2020-04659-1-4
FINAL 15 June 2022. This is the Product Information that was approved with the submission described in this
AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at
<<https://www.tga.gov.au/product-information-pi>>

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

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