# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

ENHERTU 100 mg, powder for concentrate for solution for infusion

## 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).

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.

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Infusion, powder for concentrate

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 previously received:

- trastuzumab and a taxane for metastatic disease, or
- one prior anti-HER2-based regimen and developed disease recurrence during or within six months of completing neo-adjuvant or adjuvant therapy.

### 4.2 DOSE 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.

**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.

## Premedication

ENHERTU is emetogenic [see Section 4.8 Adverse effects (undesirable effects)], which includes delayed nausea and/or vomiting. Prior to each dose of ENHERTU, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

## 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:<br>• if resolved in 28 days or less from date of onset, maintain dose.<br>• if resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1).<br>• consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*). |
| | Symptomatic ILD/Pneumonitis (Grade 2 or greater) | • Permanently discontinue ENHERTU.<br>• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*). |
| Neutropenia | Grade 3 (less than 1.0-0.5 x $10^9$/L) | • Interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. |

| Adverse Reaction | Severity | Treatment Modification | |
|---|---|---|---|
| | Grade 4 (less than 0.5 x $10^9$/L) | • Interrupt ENHERTU until resolved to Grade 2 or less.<br>• Reduce dose by one level (see Table 1). | |
| Febrile Neutropenia | Absolute neutrophil count of less than 1 x $10^9$/L and temperature greater than 38.3°C or a sustained temperature of 38°C or greater for more than one hour. | • Interrupt ENHERTU until resolved.<br>• 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% | • Continue treatment with ENHERTU. | |
| | LVEF 40% to 45% | And absolute decrease from baseline is less than 10% | • Continue treatment with ENHERTU.<br>• Repeat LVEF assessment within 3 weeks. |
| | | And absolute decrease from baseline is 10% to 20% | • Interrupt ENHERTU.<br>• Repeat LVEF assessment within 3 weeks.<br>• If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU.<br>• 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% | • Interrupt ENHERTU.<br>• Repeat LVEF assessment within 3 weeks.<br>• 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) | • 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 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. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Patients with moderate or severe renal impairment should be monitored carefully (see Section 4.4 Special warnings and precautions for use/ *Interstitial lung disease/pneumonitis*).

Hepatic impairment

No dose adjustment is required in patients with mild (total bilirubin ≤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.

For instructions on reconstitution and dilution of ENHERTU before administration, see section 6.6.

***Administration***

- If the prepared infusion solution was stored refrigerated (2ºC to 8ºC), 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. Do not administer as an intravenous push or bolus.
- 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.

## 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

### 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)].

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 .

In clinical studies, of the 491 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 12.6% of patients as determined by independent review. Most ILD cases were Grade 1 (2.9%), Grade 2 (7.7%), or Grade 3 (0.6%). Fatal outcomes occurred in 1.4% of patients treated with ENHERTU. Median time to first onset was 5.5 months (range: 1.1 to 20.8).

### 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 Dose and method of administration).

Of the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 38.1% of patients and 19.6% had Grade 3 or 4 events. Median time to first onset of decreased neutrophil count was 22 days (range: 6 to 664). Febrile neutropenia was reported in 1.2% of patients.

### Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies. LVEF should be assessed 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 Dose and method of administration).

In the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, 13 cases (2.6%) 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.

### 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 can also cause embryo-foetal 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 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 Fertility, pregnancy and lactation).

## 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

### 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 $IC_{50}$ 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.

### 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.

### Pregnancy

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.

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.

### Breast-feeding

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.

### 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 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 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

*DESTINY-Breast03*

The safety of ENHERTU was evaluated in DESTINY-Breast03 in 257 patients with unresectable or metastatic HER2-positive breast cancer (see Section 5.1 Pharmacodynamic properties/ *Clinical trials*). The median duration of treatment was 14.3 months (range: 0.7 to 29.8) in the ENHERTU group and 6.9 months (range: 0.7 to 25.1) in the trastuzumab emtansine group.

In DESTINY-Breast03 (N=257), the most common adverse reactions (frequency ≥20%) were nausea (75.9%), fatigue (49.4%), vomiting (49.0%), neutropenia (42.8%), alopecia (37.0%), constipation (34.2%), anaemia (32.7%), transaminases increased (31.5%), musculoskeletal pain (31.1%), leukopenia (30.4%), decreased appetite (29.2%), diarrhoea (29.2%), thrombocytopenia (25.7%), headache (21.8%), and abdominal pain (21.0 %). The most common serious adverse reactions (frequency >1%) were interstitial lung disease (2.3%) and vomiting (1.9%).

In DESTINY-Breast03, dose interruptions due to adverse reactions occurred in 34.2% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia (16.7%), leukopenia (5.1%), thrombocytopenia (4.3%), fatigue (4.3%), anaemia (3.5%), nausea (3.1%), and interstitial lung disease (2.7%). Dose reductions occurred in 19.8% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea (6.2%), neutropenia (3.5%), and fatigue (3.1%). Discontinuation of therapy due to an adverse reaction occurred in 10.5% of patients treated with ENHERTU. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD (8.2%).

**Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients in DESTINY-Breast03**

| Adverse Reactions | ENHERTU 5.4 mg/kg N=257 | | trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 76 | 7 | 30 | 0.4 |
| Vomiting | 49 | 1.6 | 10 | 0.8 |
| Constipation | 34 | 0 | 20 | 0 |
| Diarrhoea | 29 | 1.2 | 7 | 0.4 |
| Abdominal pain[a] | 21 | 0.8 | 8 | 0.4 |
| Stomatitis[b] | 20 | 0.8 | 5 | 0 |
| Dyspepsia | 11 | 0 | 6 | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue[c] | 49 | 6 | 35 | 0.8 |
| **Blood and Lymphatic System Disorders** | | | | |

| Adverse Reactions | ENHERTU 5.4 mg/kg N=257 | | trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| Anaemia[a] | 33 | 7 | 17 | 6 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Alopecia[e] | 37 | 0.4 | 3.1 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Musculoskeletal pain[f] | 31 | 1.2 | 25 | 0.4 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 29 | 1.6 | 17 | 0.4 |
| **Investigations** | | | | |
| Weight decreased | 17 | 1.2 | 6 | 0.4 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Epistaxis | 11 | 0 | 16 | 0.4 |
| Cough | 11 | 0.4 | 10 | 0 |
| Interstitial lung disease[g] | 11 | 0.8[h] | 1.9 | 0 |
| **Nervous System Disorders** | | | | |
| Headache[i] | 22 | 0.4 | 16 | 0 |
| Dizziness | 13 | 0.4 | 8 | 0 |

Events were graded using NCI CTCAE version 5.0. N = number of patients exposed; PT = preferred term.
Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.
Grouped term of abdominal pain includes PTs of abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.
Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption.
Grouped term of fatigue includes PTs of fatigue, asthenia, malaise, and lethargy.
Grouped term of anaemia includes PTs of anaemia, haemoglobin decreased, and red blood cell count decreased.
This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.
Grouped term of musculoskeletal pain includes PTs of back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort.
Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.
No Grade 4 or Grade 5 ILD events were adjudicated as drug-related in either arm.
Grouped term of headache includes PTs of headache, migraine.

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

- Respiratory, Thoracic and Mediastinal Disorders: dyspnoea (8%)
- Skin and Subcutaneous Tissue Disorders: pruritus (8%) and skin hyperpigmentation (6%) [grouped term includes PTs of skin hyperpigmentation, skin discoloration, and pigmentation disorder].
- Nervous System Disorders: dysgeusia (6%)
- Metabolism and Nutrition Disorders: dehydration (4.3%)
- Eye Disorders: vision blurred (3.5%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.3%) [grouped term includes PTs of hypersensitivity, infusion-related reactions]
- Blood and Lymphatic System Disorders: febrile neutropenia (0.8%)

**Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03**

| Laboratory Parameter | ENHERTU 5.4 mg/kg N=257 | | trastuzumab emtansine 3.6 mg/kg N=261 | |
|---|---|---|---|---|
| | All Grades % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Haematology** | | | | |
| White blood cell count decreased | 74 | 8 | 24 | 0.8 |
| Neutrophil count decreased | 70 | 18 | 30 | 2.3 |
| Haemoglobin decreased | 64 | 7 | 38 | 6 |
| Lymphocyte count decreased | 55 | 14 | 23 | 3.9 |
| Platelet count decreased | 52 | 7 | 79 | 24 |
| **Chemistry** | | | | |
| Aspartate aminotransferase increased | 67 | 0.8 | 83 | 5 |
| Alanine aminotransferase increased | 53 | 1.6 | 67 | 6 |
| Blood alkaline phosphatase increased | 49 | 0.8 | 46 | 0.8 |
| Hypokalaemia | 35 | 4.7 | 39 | 1.5 |
| Blood bilirubin increased | 20 | 0 | 14 | 0 |
| Blood creatinine increased | 16 | 0.8 | 8 | 0.4 |

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

*DESTINY-Breast01 and Study DS8201-A-J101*

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 5 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 ≥20%) were nausea, fatigue, vomiting alopecia, constipation, decreased appetite, anaemia, neutropenia, diarrhoea, thrombocytopaenia, cough, leukopenia, and headache (see Table 5). 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, thrombocytopaenia, hypokalaemia, ILD, diarrhoea, febrile neutropenia, dyspnoea, abdominal pain, decreased appetite, and alanine aminotransferase increased (see Table 5). 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%), thrombocytopaenia (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 5: Adverse Drug Reactions Reported in DESTINY-Breast01 and DS8201-A-J101 Trials (occurred in ≥ 10% of subjects for All Grades or ≥ 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) |
| 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) |
| Thrombocytopaenia[h] | 54 (23.1) | 10 (4.3) |

| System Organ Class[a] | ENHERTU 5.4 mg/kg N=234 | |
|---|---|---|
| | All Grades n (%) | Grades 3 or 4 n (%) |
| 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 |
| **Infections and infestations** | | |
| Upper respiratory tract infection[m] | 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 thrombocytopaenia includes PTs of thrombocytopaenia 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.
[m] Grouped term of upper respiratory tract infection 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 6: 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, 2.1% (27/1311) of evaluable patients developed antibodies against trastuzumab deruxtecan following treatment with ENHERTU. The incidence of neutralizing antibodies against trastuzumab deruxtecan was 0.1% (1/1311). There was no association between development of antibodies and allergic-type reactions

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

## 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

# 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

Trastuzumab deruxtecan, is a HER2-targeted antibody-drug conjugate (ADC). The antibody is a humanised 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 Efficacy and Safety

Metastatic Breast Cancer

*DESTINY-Breast03*

The efficacy and safety of ENHERTU were demonstrated in a Phase 3, randomised, multicentre, open-label, active-controlled study: DESTINY-Breast03.

The study included adult patients with unresectable or metastatic HER2-positive 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) by intravenous infusion 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 assessed by blinded independent central review (BICR) based on RECIST v1.1. Overall survival (OS) was a key secondary efficacy outcome measure. PFS based on investigator assessment and confirmed objective response rate (ORR) were among some of the secondary endpoints.

Demographic and baseline disease characteristics were similar between treatment arms. Of the 524 patients randomised, the median age was 54 years (range 20 to 83); 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%.

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 randomised to ENHERTU compared to trastuzumab emtansine. Overall survival (OS) was immature at the time of analysis and median OS was not reached.

Efficacy results are summarised in Table 7 and Figure 1 and Figure 2.

**Table 7 Efficacy Results in DESTINY-Breast03 (Intent-to-Treat [ITT] Analysis Set)**

| Efficacy Parameter | ENHERTU 5.4 mg/kg N=257 | trastuzumab emtansine 3.6 mg/kg N=261 |
|---|---|---|
| **PFS per 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)** | | |
| Number of events (%) | 33 (12.6) | 53 (20.2) |
| Survival at 12 months (95% CI) | 94.1% (90.3, 96.4) | 85.9% (80.9, 89.7) |
| 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) |

CI = confidence interval; NR= not reached, NE=not estimable, HR=hazard ratio
†presented as 6 decimal places

**Figure 1 Kaplan-Meier Plot of Progression-free Survival Per BICR (Intent-to-Treat Analysis Set)**

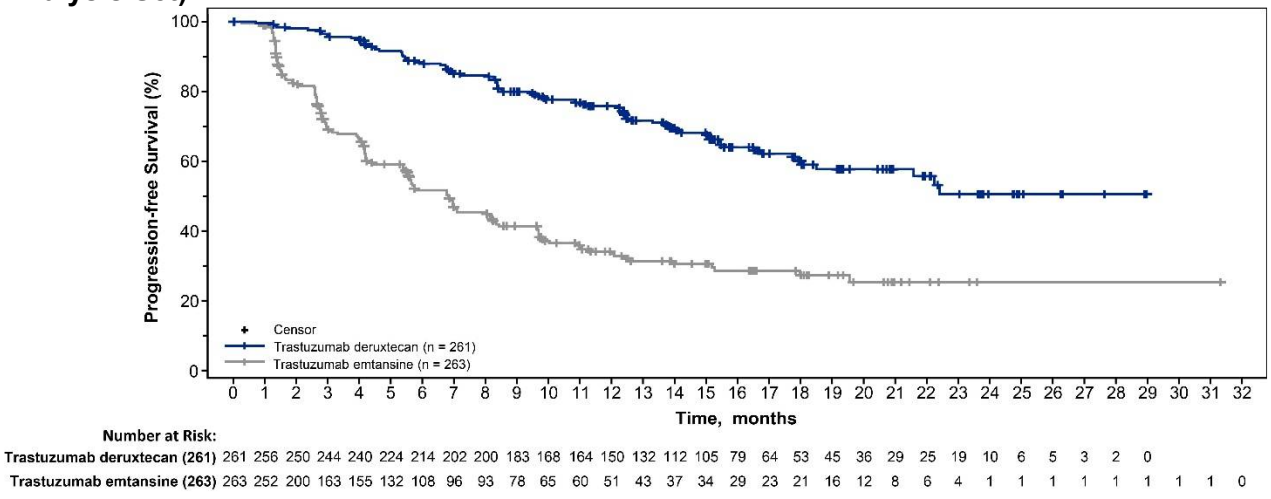
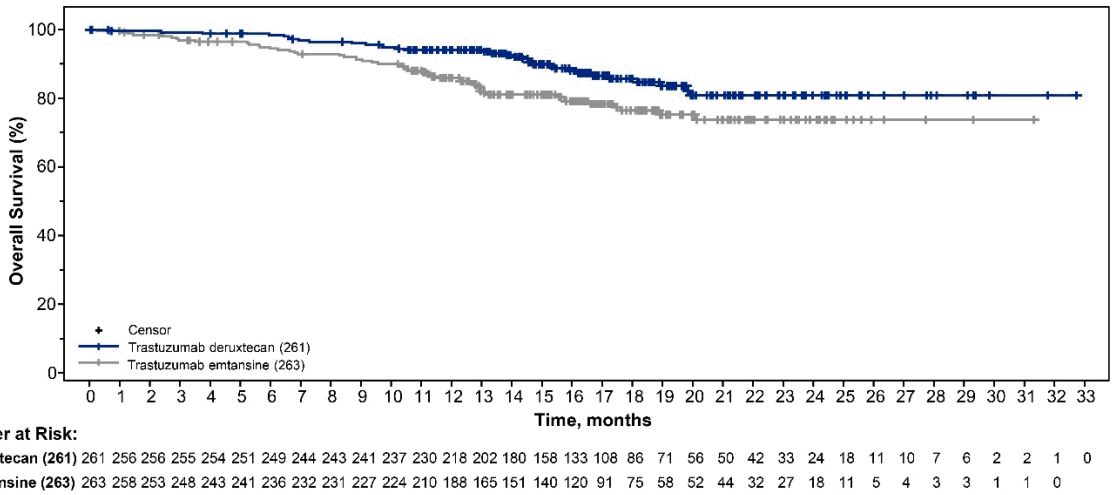



**Figure 2 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Analysis Set)**




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

*DESTINY-Breast01*

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 summarised in Table 8.

**Table 8: 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 ≥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]%) Cmax of trastuzumab deruxtecan and DXd were 131 µg/mL (20%) and 4.4 ng/mL (41%), respectively, and the AUC of trastuzumab deruxtecan and DXd were 770 µg·day/mL (28%) and 27 ng·day/mL (40%), respectively, based on population pharmacokinetic analysis.

### Distribution

Based on population pharmacokinetic analysis, the volume of distribution of the central compartment (Vc) of trastuzumab deruxtecan was estimated to be 2.71 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.

### Biotransformation

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

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

### Elimination

Based on population pharmacokinetic analysis, following intravenous administration of trastuzumab deruxtecan, the clearance of trastuzumab deruxtecan was estimated to be 0.42 L/day and the clearance of the topoisomerase I inhibitor was 19.4 L/h. The apparent elimination half-life (t1/2) 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.

### Special Populations

#### Age, race, ethnicity, sex and body weight

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 topoisomerase I inhibitor.

#### Renal impairment

No dedicated renal impairment study was conducted. Based on population pharmacokinetic analysis including patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥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 (CLcr ≥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

### Animal Toxicology and/or Pharmacology

In a six-week repeat-dose toxicity study, trastuzumab deruxtecan was administered to rats once every three weeks at doses up to 197 mg/kg (approximately 31 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, lymphatic/hematopoietic organs (thymus, lymph nodes, bone marrow), kidneys, skin, testes, and incisor teeth. All

changes observed, except for testicular and incisor teeth changes, were reversible following a nine-week recovery period.

In a three-month repeat-dose toxicity study, trastuzumab deruxtecan was administered to monkeys once every three weeks at doses up to 30 mg/kg (approximately 9 times the clinical dose of 5.4 mg/kg based on AUC). Toxicities were observed in intestines, testes, skin, bone marrow, kidneys, and lungs. Pulmonary toxicity was observed at the highest dose (30 mg/kg) and histopathologically characterized by aggregation of foamy alveolar macrophages and focal alveolus and/or interstitial inflammation which showed reversibility after a three-month recovery period. Changes observed in other organs, except for those in the skin and kidney, also showed reversibility or a trend toward reversibility by the end of a three-month recovery period.

### Mutagenesis/Carcinogenesis

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 studies have not been conducted with trastuzumab deruxtecan.

### Impairment of Fertility and Teratogenicity

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/hematopoietic organs, intestine, or testes), and the topoisomerase I inhibitor 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.

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

36 months

### 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 2ºC to 8ºC 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 2ºC to 8ºC for up to 24 hours, protected from light. These storage times start from the time of dilution.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials in a refrigerator (2ºC to 8ºC) 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 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.
- 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.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2ºC to 8ºC 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:

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

- Withdraw the calculated amount from the vial(s) using a sterile syringe. 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.
- 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 2ºC to 8ºC for up to 24 hours, protected from light. Do not freeze.
- Discard any unused portion left in the vial.

***Disposal***

The reconstituted product contains no preservative and is intended for single use only.

Discard any unused portion left in the vial.

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

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

## 9. DATE OF FIRST APPROVAL

7 December 2023

## 10. DATE OF REVISION OF THE TEXT

7 December 2023

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