

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 ENHERTU™

Trastuzumab deruxtecan for injection

Powder for concentrate for solution for infusion, 100 mg, Intravenous infusion

Professed

Antineoplastic Agent (L01XC41)

ENHERTU (trastuzumab deruxtecan), indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1), has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ENHERTU, please refer to Health Canada's [Notice of Compliance with conditions - drug products](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php) web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>.

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**This product has been authorized under the
Notice of Compliance with Conditions (NOC/c)
for one or all of its indicated uses.**

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

RECENT MAJOR LABEL CHANGES

Not Applicable.

TABLE OF CONTENTS

| | |
|---|-----------|
| RECENT MAJOR LABEL CHANGES | 3 |
| TABLE OF CONTENTS | 3 |
| PART I: HEALTH PROFESSIONAL INFORMATION | 5 |
| 1 INDICATIONS | 5 |
| 1.1 Pediatrics | 5 |
| 1.2 Geriatrics | 5 |
| 2 CONTRAINDICATIONS | 5 |
| 3 SERIOUS WARNINGS AND PRECAUTIONS BOX | 6 |
| 4 DOSAGE AND ADMINISTRATION | 6 |
| 4.1 Dosing Considerations | 6 |
| 4.2 Recommended Dose and Dosage Adjustment | 6 |
| 4.3 Administration | 9 |
| 4.4 Reconstitution..... | 9 |
| 4.5 Missed Dose | 10 |
| 5 OVERDOSAGE | 10 |
| 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING | 10 |
| 7 WARNINGS AND PRECAUTIONS | 11 |
| 7.1 Special Populations..... | 13 |
| 7.1.1 Pregnant Women..... | 13 |
| 7.1.2 Breast-feeding | 13 |
| 7.1.3 Pediatrics..... | 13 |
| 7.1.4 Geriatrics..... | 13 |
| 8 ADVERSE REACTIONS | 14 |
| 8.1 Adverse Reaction Overview..... | 14 |
| 8.2 Clinical Trial Adverse Reactions..... | 14 |
| 8.3 Less Common Clinical Trial Adverse Reactions..... | 16 |
| 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data..... | 17 |
| 9 DRUG INTERACTIONS | 18 |
| 9.1 Drug-Drug Interactions | 18 |
| 9.2 Drug-Food Interactions | 18 |
| 9.3 Drug-Herb Interactions | 18 |
| 9.4 Drug-Laboratory Test Interactions | 18 |
| 10 ACTION AND CLINICAL PHARMACOLOGY | 18 |
| 10.1 Mechanism of Action | 18 |

| | | |
|---|---|-----------|
| 10.2 | Pharmacodynamics..... | 19 |
| 10.3 | Pharmacokinetics | 19 |
| 11 | STORAGE, STABILITY AND DISPOSAL..... | 22 |
| 12 | SPECIAL HANDLING INSTRUCTIONS | 22 |
| PART II: SCIENTIFIC INFORMATION..... | | 23 |
| 13 | PHARMACEUTICAL INFORMATION | 23 |
| 14 | CLINICAL TRIALS | 24 |
| 14.1 | Trial Design and Study Demographics..... | 24 |
| 14.2 | Study Results..... | 24 |
| 15 | NON-CLINICAL TOXICOLOGY | 25 |
| PATIENT MEDICATION INFORMATION | | 27 |

ENHERTU (trastuzumab deruxtecan), indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1),

has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

For further information for ENHERTU, please refer to Health Canada's [Notice of Compliance with conditions - drug products](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php) web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>.

PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c 1 INDICATIONS

ENHERTU (trastuzumab deruxtecan) as monotherapy is indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1).

The indication is authorized based on tumour response rate and durability of response. An improvement in survival has not been established. See CLINICAL TRIALS.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No clinically relevant differences in efficacy were observed between patients ≥ 65 years and those younger than 65 years. Evidence from clinical studies suggests the use in the geriatric population is associated with differences in safety. See WARNINGS AND PRECAUTIONS, Special Populations.

NOC/c 2 CONTRAINDICATIONS

ENHERTU (trastuzumab deruxtecan) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU (trastuzumab deruxtecan). Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Administration and WARNINGS AND PRECAUTIONS).
- Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception (see WARNINGS AND PRECAUTIONS, Special Populations).
- There is a risk of medication errors between ENHERTU (trastuzumab deruxtecan) and trastuzumab or trastuzumab emtansine (T-DM1). See DOSAGE AND ADMINISTRATION, Dosing Considerations.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

ENHERTU should only be used in patients with documented HER2-positive tumour status (see CLINICAL TRIALS).

There is a risk of medication errors between ENHERTU (trastuzumab deruxtecan) and trastuzumab or trastuzumab emtansine (T-DM1). 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 (T-DM1).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

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

The initial dose should be administered as a 90 minute intravenous infusion. If the prior infusion was well tolerated, subsequent doses of ENHERTU may be administered as 30 minute infusions.

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-related reactions.

Dosage Adjustment

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 ^a | 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 WARNINGS AND PRECAUTIONS). |
| | Symptomatic ILD/ pneumonitis (Grade 2 or greater) | <ul style="list-style-type: none"> Permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/ pneumonitis is suspected (see WARNINGS AND PRECAUTIONS). |
| 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 | <ul style="list-style-type: none"> Interrupt ENHERTU until resolved. Reduce dose by one level (see Table 1). |

| Adverse Reaction | Severity ^a | | Treatment Modification |
|---|---|--|--|
| | temperature of 38°C or greater for more than one hour. | | |
| Left Ventricular Ejection Fraction (LVEF) Decreased | LVEF greater than 45% and absolute decrease from baseline is 10% to 20% | | <ul style="list-style-type: none"> Continue treatment with ENHERTU. |
| | LVEF 40% to 45% | And absolute decrease from baseline is less than 10% | <ul style="list-style-type: none"> Continue treatment with ENHERTU. Repeat LVEF assessment within 3 weeks. |
| | | And absolute decrease from baseline is 10% to 20% | <ul style="list-style-type: none"> Interrupt ENHERTU. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. |
| | LVEF less than 40% or absolute decrease from baseline is greater than 20% | | <ul style="list-style-type: none"> Interrupt ENHERTU. Repeat LVEF assessment within 3 weeks. If LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed, permanently discontinue ENHERTU. |
| | Symptomatic congestive heart failure (CHF) | | <ul style="list-style-type: none"> Permanently discontinue ENHERTU. |

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

Special Populations

Pediatrics (<18 years of age): 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 pediatric population for the indication of metastatic breast cancer.

Geriatrics (≥65 years of age): No dose adjustment of ENHERTU is required in patients aged 65 years or older.

Renal Impairment: No dose adjustment is required in patients with mild (creatinine clearance [CrCL] ≥60 and <90 mL/min) or moderate (CrCL ≥30 and <60 mL/min) renal impairment at baseline. A higher incidence of adverse events leading to dosage discontinuation or reduction (including ILD) was observed in patients with moderate renal impairment. Patients with

moderate renal impairment should be closely monitored. 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 at baseline. 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 $>$ ULN) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment.

4.3 Administration

ENHERTU is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion. Administer ENHERTU as an intravenous infusion only with a 0.20 or 0.22 micron in line polyethersulfone (PES) or polysulfone (PS) filter. ENHERTU must NOT be administered as an intravenous push or bolus.

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.

Do not mix ENHERTU with other medicinal products or administer other medicinal products through the same intravenous line.

See SPECIAL HANDLING INSTRUCTIONS for additional recommendations.

4.4 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 colorless 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.

Table 3 Reconstitution

| Vial Size | Volume of Diluent to be Added to Vial | Approximate Available Volume | Nominal Concentration per mL |
|-----------|---------------------------------------|------------------------------|------------------------------|
| 100 mg | 5 mL | 5mL | 20 mg/mL |

Instructions for 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.** 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.

4.5 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.

5 OVERDOSAGE

There is limited information on overdose with trastuzumab deruxtecan. In clinical studies, the highest dose administered was 8.0 mg/kg. Incidence of severe adverse events appeared higher in patients administered doses higher than the recommended dose. In the event of overdose, patients should be monitored, and appropriate supportive care should be given. There is no antidote for trastuzumab deruxtecan.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4 Dosage Forms, Strengths, Composition and Packaging.

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|---|---|
| Intravenous infusion | Powder for concentrate for solution for infusion/100 mg/ vial | L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose |

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box.

Cardiovascular

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 (trastuzumab deruxtecan) 5.4 mg/kg, three cases (1.3%) of asymptomatic LVEF decrease were reported as adverse events, of which 2 (0.9%) were Grade 2 and 1 (0.4%) was Grade 3 (see ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions). Grade 2 LVEF decrease as abnormal laboratory findings was also observed (see ADVERSE REACTIONS, Abnormal Laboratory Findings). No decreases of LVEF to less than 40% were observed. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or 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 DOSAGE AND ADMINISTRATION).

Driving and Operating Machinery

ENHERTU may impair the ability to drive and use machines as adverse reactions including fatigue, headache and dizziness have been reported. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

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 (see ADVERSE REACTIONS).

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 DOSAGE AND ADMINISTRATION).

Immune

Infusion-Related Reactions

Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity were reported in clinical studies of ENHERTU (see ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions). ENHERTU has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Patients should be monitored for IRRs. ENHERTU may require dose interruption or

discontinuation, based on the severity of the IRR (see DOSAGE AND ADMINISTRATION).

Respiratory

Interstitial Lung Disease/ Pneumonitis

Cases of interstitial lung disease (ILD), and/or pneumonitis, have been reported with ENHERTU (see ADVERSE REACTIONS). 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, dyspnea, 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 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 DOSAGE AND ADMINISTRATION). 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 or until complete resolution of clinical and chest computed (CT) findings. Then gradually taper for at least 4 weeks. ENHERTU should be permanently discontinued in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD/ pneumonitis (see DOSAGE AND ADMINISTRATION). Patients with a history of ILD/pneumonitis may be at increased risk of developing ILD/pneumonitis.

Sexual Health

Reproduction

ENHERTU can cause fetal harm when administered to a pregnant woman. Exposure to ENHERTU to a pregnant woman should be avoided (see Special Populations, Pregnant Women).

Pregnancy Testing

Pregnancy status of females of reproductive potential should be verified prior to initiation of ENHERTU (see Special Populations).

Contraception in Males and Females

Female patients of reproductive potential should be informed of the potential risks to the fetus. Females patients of reproductive potential should be advised to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose (see Special Population).

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 following the last dose.

Fertility

No fertility studies in women and men have been conducted with ENHERTU. Based on results from animal toxicity studies, ENHERTU may impair male reproductive function and fertility (see NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU 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 ENHERTU can also cause embryo fetal harm when administered to a pregnant woman (see NON-CLINICAL TOXICOLOGY).

ENHERTU should not be administered to pregnant women and patients should be informed of the potential risks to the fetus before they become pregnant. If a patient becomes pregnant during treatment with ENHERTU or within 7 months following the last dose of ENHERTU, the patient must immediately contact her doctor and should be apprised of the possibility of harm to the fetus. See WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction for recommendations on pregnancy test and contraception.

7.1.2 Breast-feeding

There are no data regarding the presence of ENHERTU in human milk. As human IgG is excreted in human milk, ENHERTU, a humanized IgG1 conjugated to deruxtecan (see PHARMACEUTICAL INFORMATION), may be excreted in human milk. 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 234 patients with HER2 positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall difference in efficacy was observed based on age. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (49%) as compared to younger patients (39%).

Population pharmacokinetic analysis indicates that age does not have an effect on the parameters of population pharmacokinetics of trastuzumab deruxtecan.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of ENHERTU (trastuzumab deruxtecan) was 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. The most common adverse reactions (frequency $\geq 20\%$) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutrophil count decreased, diarrhea, cough, leukopenia, headache and platelet count decreased (Table 5). Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were interstitial lung disease, vomiting, nausea, and hypokalemia. Fatalities due to adverse events occurred in 5.1% of patients including interstitial lung disease (2.6%).

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%), anemia (3.4%), upper respiratory tract infection (3.0%), leukopenia (3.0%), interstitial lung disease (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 interstitial lung disease (9.4%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 (see CLINICAL TRIALS). The median duration of treatment was 9.8 months (range: 0.7 to 37.1). Table 5 lists adverse drug reactions, with incidences regardless of investigators assessment of causality, reported in this patient population.

Table 5 Adverse Drug Reactions Reported in DESTINY-Breast01 and DS8201-A-J101 Trials ($\geq 10\%$ All Grades or $\geq 2\%$ Grades 3 or 4)

| System Organ Class ^a | ENHERTU 5.4 mg/kg N=234 | |
|---|----------------------------|------------------------|
| | All Grades n (%) | Grades 3 or 4 n (%) |
| Blood and Lymphatic System Disorders | | |
| Anemia ^b | 79 (33.8) | 21 (9.0) |
| Neutropenia ^c | 76 (32.5) | 44 (18.8) |

| System Organ Class ^a | ENHERTU 5.4 mg/kg N=234 | |
|---|----------------------------|------------------------|
| | All Grades n (%) | Grades 3 or 4 n (%) |
| Thrombocytopenia ^d | 54 (23.1) | 10 (4.3) |
| Leukopenia ^e | 48 (20.5) | 13 (5.6) |
| Lymphopenia ^f | 26 (11.1) | 12 (5.1) |
| Eye disorders | | |
| Dry eye | 27 (11.5) | 1 (0.4) |
| Gastrointestinal Disorders | | |
| Nausea | 187 (79.9) | 16 (6.8) |
| Vomiting | 114 (48.7) | 10 (4.3) |
| Constipation | 84 (35.9) | 2 (0.9) |
| Diarrhea | 72 (30.8) | 6 (2.6) |
| Abdominal Pain ^g | 46 (19.7) | 3 (1.3) |
| Stomatitis ^h | 35 (15.0) | 2 (0.9) |
| Dyspepsia | 33 (14.1) | 0 |
| General Disorders and Administration Site Conditions | | |
| Fatigue ⁱ | 141 (60.3) | 15 (6.4) |
| Infections and infestations | | |
| Upper respiratory tract infections ^j | 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) |
| Nervous System Disorders | | |
| Headache ^k | 47 (20.1) | 0 |
| Dizziness | 25 (10.7) | 0 |
| Metabolism and Nutrition Disorders | | |
| Decreased appetite | 81 (34.6) | 3 (1.3) |

| System Organ Class ^a | ENHERTU 5.4 mg/kg N=234 | |
|--|----------------------------|------------------------|
| | All Grades n (%) | Grades 3 or 4 n (%) |
| Hypokalemia | 30 (12.8) | 8 (3.4) |
| Respiratory, Thoracic and Mediastinal Disorders | | |
| Cough | 50 (21.4) | 0 |
| Dyspnea | 34 (14.5) | 4 (1.7) |
| Epistaxis | 33 (14.1) | 0 |
| Interstitial lung disease ^l | 32 (13.7) | 1 (0.4) |
| Skin and Subcutaneous Tissue Disorders | | |
| Alopecia | 108 (46.2) | 1 (0.4) |
| Rash ^m | 30 (12.8) | 1 (0.4) |

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

^a Based on MedDRA version 20.1; events were graded using NCI-CTCAE version 4.03.

^b Grouped term of anemia includes PTs of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased.

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

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

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

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

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

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

ⁱ Grouped term of fatigue includes PTs of fatigue and asthenia.

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

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

^l 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; includes 6 (2.6%) fatal events.

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

8.3 Less Common Clinical Trial Adverse Reactions

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

Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

Cardiac Disorders: ejection fraction decrease (1.3%)

Infections and Infestations: sepsis (0.9%)

Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 % |
| Hematology | | |
| White blood cell count decreased | 168 (72.4) | 20 (8.6) |
| Anemia | 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) |
| Hypokalemia | 64 (27.8) | 9 (3.9) |

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

Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) laboratory measurements (ECHO/MUGA) were conducted at baseline and every 2 cycles in Study DS8201-A-J101 and every 4 cycles in Study DESTINY-Breast01. A total of 37/219 (16.9%) patients in the HER2-positive 5.4 mg/kg Pool met the criteria for a Grade 2 LVEF decrease (NCI-CTCAE version 4.03). Twenty-three of these 37 patients subsequently recovered to within 90% of baseline value.

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. Due to the limited number of patients who tested positive for anti-drug antibody, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety. In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Effects of Other Medicinal Products on the Pharmacokinetics of ENHERTU

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 ENHERTU (trastuzumab deruxtecan) or the released topoisomerase I inhibitor. No dose adjustment is required during coadministration of ENHERTU with drugs that are inhibitors of OATP1B or CYP3A.

No clinically meaningful interaction is expected with drugs that are inhibitors of P glycoprotein (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 component of ENHERTU does not inhibit or induce major CYP450 enzymes.

9.2 Drug-Food Interactions

Interactions with food have not been established.

9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ENHERTU (trastuzumab deruxtecan) is a HER2 targeted 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. Stability studies have demonstrated that < 5% of the intact ADC dissociates into the DXd form within 21 days.

Following binding to HER2 on tumor cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane permeable topoisomerase I inhibitor causes DNA damage and apoptotic cell death.

The antibody is produced in Chinese hamster ovary cells by recombinant DNA technology and

NOC/c

the topoisomerase I inhibitor and linker are produced by chemical synthesis. Approximately 8 molecules of deruxtecan are attached to each antibody molecule.

10.2 Pharmacodynamics

Cardiac Electrophysiology

In a phase 1, open-label, single-arm study of ENHERTU administered to patients with unresectable and/or metastatic HER2-expressing breast cancer, no large mean increase from baseline in QTc interval (i.e. >20 ms) was detected following treatment with ENHERTU at 6.4 mg/kg every 3 weeks (1.2 fold higher than recommended dose) on Cycle 1 or Cycle 3, 7 hours postdose (N=49).

10.3 Pharmacokinetics

The pharmacokinetics of trastuzumab deruxtecan was evaluated in patients with cancer. Following a single dose, exposures (C_{max} and AUC) of trastuzumab deruxtecan and released topoisomerase inhibitor (DXd) increased proportionally over a dose range of 3.2 mg/kg to 8 mg/kg (approximately 0.6 to 1.5 times the recommended dose).

Table 7 PK parameters following administration of 5.4 mg/kg dose of trastuzumab deruxtecan based on a noncompartmental analysis in HER2 positive breast cancer patients

| | Cmax (ug/mL ^a or ng/mL ^b) | Ctrough (ug/mL ^a or ng/mL ^b) | AUCinf (ug/mL*day ^a or ng/mL*day ^b) | AUC(tau) (ug/mL*day ^a or ng/mL*day ^b) | CL (mL/day /kg) ^c | Vss (L) ^c | half-lives (days) | Tmax^c (hours) | Accumulation Ratio^d |
|---------------------------|---|--|---|--|---|--------------------------------|-----------------------------|------------------------------------|---|
| Trastuzumab deruxtecan | 124 (32.6) [N=232] | 5.5 (5.1) [N=215] | 609 (203) [N=50] | 573 (167) [N=190] | 10.4 (3.5) [N=212] | 3.66 (0.93) [N=212] | 5.6 (1.2) [N=50] | 2.2 (0.02 - 167) [N=232] | 1.35 (0.15) [N=51] |
| DXd | 8.2 (5.7) [N=232] | 0.26 (0.25) [N=226] | 36.4 (12.8) [N=45] | 33.3 (16.6) [N=109] | ND | ND | 5.6 (1.3) [N=45] | 6.8 (0.24 - 167) [N=232] | 1.09 (0.194) [N=51] |

Table shows arithmetic mean (standard deviation) values of PK parameters in Cycle 1;

AUCinf = area under the concentration-time curve from time 0 to infinity; AUC(tau) = area under the serum concentration-time curve during the dosing interval; CL = clearance; Cmax = maximum observed serum concentration; Ctrough = trough serum concentration; DXd = released topoisomerase inhibitor; ND = Not determined (since DXd could not be estimated as an administered dose, Vss and CL for DXd were not estimated) Tmax = time of maximum observed serum concentration; Vss = volume of distribution at steady state.

a. For trastuzumab deruxtecan

b. For DXd

c. Values reported are median (range)

d. The accumulation ratio of trastuzumab deruxtecan and DXd for AUC(tau) at Cycle 3 vs Cycle 1 were determined following administration of 6.4 mg/kg dose

Distribution: Based on noncompartmental analysis, the volume of distribution at steady state (V_{ss}) is 3.66L.

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.

Elimination: Based on noncompartmental analysis, following intravenous administration of trastuzumab deruxtecan in patients with metastatic HER2 positive breast cancer, the clearance parameter of trastuzumab deruxtecan was estimated to be 10.4 mL/day/kg. The apparent elimination half life (t_{1/2}) of trastuzumab deruxtecan and released topoisomerase I inhibitor was approximately 5.6 days. *In vitro*, topoisomerase I inhibitor was a substrate of P-gp, OATP1B1, OATP1B3, MATE2 K, MRP1, and BCRP. 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 feces via the biliary route. The topoisomerase I inhibitor was the most abundant component in urine, feces, 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 feces.

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 and Conditions

Based on population pharmacokinetic analysis, age (23-96 years), race, ethnicity, sex and body weight did not have an effect on pharmacokinetic parameters of trastuzumab deruxtecan or released topoisomerase I inhibitor.

Hepatic Insufficiency: No dedicated hepatic impairment study was conducted.

Renal Insufficiency: No dedicated renal impairment study was conducted.

11 STORAGE, STABILITY AND DISPOSAL

Storage of Vials

Store ENHERTU (trastuzumab deruxtecan) vials in a refrigerator (2°C to 8°C) until time of reconstitution.

Do not freeze.

Shelf-life of 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.

Shelf-life of 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.

Disposal

See SPECIAL HANDLING INSTRUCTIONS.

12 SPECIAL HANDLING INSTRUCTIONS

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

ENHERTU is a cytotoxic drug. Appropriate procedures for the storage, preparation, administration and disposal of chemotherapeutic medicinal products should be used. Appropriate aseptic technique should be used for the reconstitution and dilution procedures.

ENHERTU (trastuzumab deruxtecan), indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1), has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ENHERTU, please refer to Health Canada's [Notice of Compliance with conditions - drug products](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php) web site: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

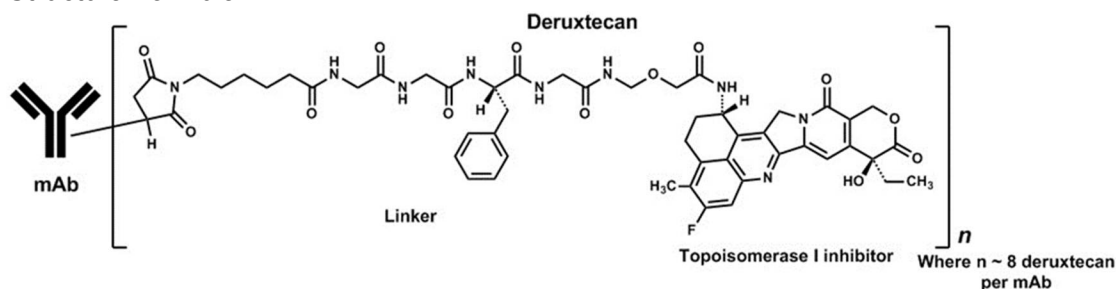
Proper name: trastuzumab deruxtecan

Chemical name: Immunoglobulin G1-kappa, anti-[Homo sapiens ERBB2 (epidermal growth factor receptor 2, receptor tyrosine-protein kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], humanized monoclonal antibody conjugated to deruxtecan, comprising a linker and a camptothecin derivative; gamma1 heavy chain (1-450) [humanized VH (Homo sapiens IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*02)[8.8.13] (1-120) -Homo sapiens IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (217) (121-218), hinge (219-233), CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (Homo sapiens IGKV1-39*01 (86.20%) - IGKJ1*01)[6.3.9] (1'-107') -Homo sapiens IGKC*01, Km3 A45.1, V101 (108'-214')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 8 cysteinyl, to deruxtecan, comprising a linker and a camptothecin derivative

Molecular formula and molecular mass: $C_{6460}H_{9972}N_{1724}O_{2014}S_{44} + H \times 8 + C_{52}H_{56}FN_9O_{13} \times 8 = C_{6876}H_{10428}F_8N_{1796}O_{2118}S_{44}$

Mass: 153,701.98 (Deglycosylated, C-term Lys(+))

Structural formula:



Physicochemical properties: Trastuzumab deruxtecan is a white to yellowish white lyophilized powder.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 8 Summary of patient demographics for clinical trials for Metastatic Breast Cancer

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|------------------|--|--|--------------------|---------------------------|-------------|
| DESTINY-Breast01 | Phase 2, single-agent, open-label, multicenter study | ENHERTU 5.4 mg/kg IV | 184 | 55 years (range 28 to 96) | 100% female |

The efficacy and safety of ENHERTU (trastuzumab deruxtecan) were demonstrated in a Phase 2, single-agent, open-label, multicenter study: DESTINY-Breast01.

The study enrolled adult patients with unresectable or metastatic HER2-positive breast cancer who had received prior treatment with trastuzumab emtansine (T-DM1). Patients had received two or more prior anti-HER2 regimens, including T-DM1 (100%), trastuzumab (100%), and pertuzumab (65.8%). Archival breast tumor samples were required to show HER2 positivity defined as HER2 Immunohistochemistry (IHC) 3+ or In-Situ Hybridization (ISH)-positive. The study excluded patients with a history of treated ILD or ILD at screening, patients with untreated, symptomatic brain metastases 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 Tumors (RECIST v1.1) in the intent-to-treat (ITT) population as evaluated by independent central review. Duration of response (DOR) was a secondary efficacy measure.

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%); stable brain metastases (13%); 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%).

14.2 Study Results

The median duration of follow-up for subjects was 11.1 months (range 0.7-19.9). The confirmed ORR was 60.9% (95% CI: 53.4, 68.0) and median DoR with confirmed response was 14.8 months (95% CI: 13.8, 16.9).

Efficacy results are summarized in [Table 9](#).

Table 9- Efficacy Results by Independent Central Review in DESTINY-Breast01 (Intent-to-Treat Analysis Set)

| Efficacy Parameter | DESTINY-Breast01 N=184 n (%) |
|---|------------------------------------|
| Confirmed Objective Response Rate (ORR) (95% CI) | 112 (60.9) (53.4, 68.0) |
| Complete Response (CR) | 11 (6.0) |
| Partial Response (PR) | 101 (54.9) |
| Duration of Response (DoR) Median [†] , months (95% CI)* | 14.8 (13.8, 16.9) |

ORR 95% CI calculated using Clopper-Pearson method

CI = confidence interval; CR = complete response; DoR = duration of response; ORR = objective response rate; PR = partial response

95% CIs calculated using Brookmeyer-Crowley method

*DOR is based on a median duration of follow-up of 11.1 months.

†Based on Kaplan-Meier estimates

NR = not reached

In DESTINY-Breast01, the subgroup of patients who received prior pertuzumab therapy had a confirmed ORR of 65% (95% CI: 55, 73), and those who did not receive prior pertuzumab therapy had a confirmed ORR of 54% (95% CI: 41, 67). The subgroup of patients who were hormone receptor positive at baseline had a confirmed ORR of 58% (95% CI: 47, 68), and those who were hormone receptor negative at baseline had a confirmed ORR of 66% (95% CI: 55, 76). The results should be interpreted with caution given the inherent risks with subgroup analyses in general.

15 NON-CLINICAL TOXICOLOGY

General Toxicology

Rats

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.

Cynomolgus Monkeys

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.

Carcinogenicity and Mutagenicity

Carcinogenicity studies have not been conducted with trastuzumab deruxtecan.

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.

Reproductive and Developmental Toxicology

Impairment of Fertility

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

Developmental Toxicity

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.

Juvenile Animal Studies

No juvenile toxicity studies have been conducted.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

 **ENHERTU™**

Trastuzumab deruxtecan for injection

Read this carefully before you start treatment with **ENHERTU** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENHERTU**.

Serious Warnings and Precautions

- Lung problems that may be severe, life-threatening or that may lead to death. Tell your healthcare provider right away if you get any of the following signs and symptoms at any time during treatment:
 - cough
 - trouble breathing or shortness of breath
 - fever
 - other new or worsening breathing symptoms (e.g., chest tightness, wheezing)If you develop lung problems your healthcare provider may treat you with corticosteroid medicines.
- Harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with **ENHERTU**.
 - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with **ENHERTU**.
 - Females who are able to become pregnant should use effective birth control (contraception) during treatment with **ENHERTU** and for at least 7 months after the last dose.Males who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with **ENHERTU** and for at least 4 months after the last dose.
- There is a risk of **ENHERTU** medication errors. Verify with your healthcare provider that you are receiving the authorized **ENHERTU** (trastuzumab deruxtecan) dose and **NOT** trastuzumab or trastuzumab emtansine.

What is ENHERTU used for?

ENHERTU is used in adults who have:

- HER2-positive breast cancer that has spread to other parts of the body (metastatic) or cannot be taken out by surgery **and**
- also received prior trastuzumab emtansine (T-DM1).

For the following indication(s) ENHERTU has been approved *with conditions* (Notice of Compliance with Conditions - NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- ENHERTU (trastuzumab deruxtecan) is used in adults who have HER2-positive breast cancer that has spread to other parts of the body (metastatic) or cannot be taken out by surgery and also received prior trastuzumab emtansine (T-DM1).

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does ENHERTU work?

ENHERTU contains the active substance trastuzumab deruxtecan, which is made up of a monoclonal antibody connected to a medicine intended to kill cancer cells. The monoclonal antibody delivers the medicine to cancer cells that express HER2 proteins (known as HER2 positive). Once ENHERTU enters the cell, the medicine becomes active and kills the cancer cells.

What are the ingredients in ENHERTU?

Medicinal ingredients: trastuzumab deruxtecan

Non-medicinal ingredients: L histidine, L histidine hydrochloride monohydrate, polysorbate 80, sucrose.

ENHERTU comes in the following dosage forms:

Vial containing 100 mg of trastuzumab deruxtecan

Do not use ENHERTU if:

- You are allergic to trastuzumab deruxtecan or to any ingredients in ENHERTU. If you are not sure, talk to your healthcare professional before you are given ENHERTU.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENHERTU. Talk about any health conditions or problems you may have, including if you:

- have or have had any lung problems, any heart problems or any blood problems (low blood count).

Other warnings you should know about:

When you first receive this medicine and anytime during treatment, immediately tell your doctor or nurse if you have:

- cough, shortness of breath, fever, or other new or worsening breathing problems. These may be symptoms of a serious and potentially fatal lung disease (interstitial lung disease [ILD]/ pneumonitis).
- chills, fever, sores in your mouth, stomach pain or pain when urinating. These may be symptoms of an infection caused by low levels of a type of white blood cell called neutrophils (neutropenia).
- new or worsening shortness of breath, cough, fatigue, swelling of your ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness. These may be symptoms of a problem with your heart's ability to pump blood (decreased left ventricular ejection fraction [LVEF]).
- chills or shaking, shortness of breath or wheezing, itching, rash or hives, flushing, dizziness, fever, feeling like passing out (infusion related reaction).

Children and adolescents

- ENHERTU is not recommended for anyone under the age of 18 years.

Pregnancy

- ENHERTU is not recommended if you are pregnant because this medicine may cause harm to the unborn baby.
- Tell your doctor before using ENHERTU if you are pregnant, think you may be pregnant or are planning to have a baby.
- Use effective contraception to avoid becoming pregnant while you are being treated with ENHERTU. Talk to your doctor about the best contraception for you.
- Females should continue to take contraception for at least 7 months after your last dose of ENHERTU. Talk to your doctor before stopping your contraception.
- Male patients with a female partner who could become pregnant should use effective contraception during treatment and for at least 4 months after the last dose of ENHERTU.
- If you do become pregnant during treatment with ENHERTU, tell your doctor right away.

Breastfeeding

- You should not breastfeed during treatment with ENHERTU.
- You should not breastfeed for at least 7 months after your last treatment of ENHERTU.
- It is not known whether the ingredients in ENHERTU pass into breast milk. Talk to your doctor about this.

Driving and using machines: ENHERTU may reduce your ability to drive or use machines. Be careful if you feel tired, dizzy or have a headache.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ENHERTU:

Enhertu will be given to you by a healthcare professional.

Usual dose:

ENHERTU will be given to you in a hospital or clinic.

- The recommended dose of ENHERTU is 5.4 mg for every kilogram of your body weight, every 3 weeks.
- Your doctor or nurse will give you ENHERTU through an infusion into your vein (IV).
- Your first infusion will be given to you over 90 minutes. If you have no problems with the first infusion, the infusion on your next visits may be given over 30 minutes.
- Your doctor will decide how many treatments you need.
- If you experience infusion related symptoms, your doctor or nurse may slow, interrupt or stop your treatment.

Overdose:

If you think you have been given too much ENHERTU, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment to get ENHERTU

- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

Do not stop treatment with ENHERTU unless you have discussed this with your doctor. If you have any further questions about your treatment, ask your doctor.

What are possible side effects from using ENHERTU?

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

While you are taking ENHERTU

- Your doctor will carry out tests before and during your treatment with ENHERTU.
- Depending on the side effects you experience, your doctor may decide to lower your dose, temporarily stop your treatment or permanently stop your treatment.

Tell your doctor right away if you notice any of the following symptoms because some of them may be signs of a serious or possibly fatal condition.

Getting medical treatment right away may help keep these problems from becoming more serious.

- cough, shortness of breath, fever, or other new or worsening breathing problems as these may be symptoms of a lung problem.

- chills, fever, sores in your mouth, stomach pain or pain when urinating as these may be symptoms of an infection.
- new onset or worsening shortness of breath, cough, fatigue, swelling of your ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness as these may be symptoms of a heart problem.

You may experience the following side effects:

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

- Nausea
- Feeling tired (fatigue)
- Vomiting
- Hair loss (alopecia)
- Constipation
- Feeling less hungry
- Diarrhea
- Coughing
- Stomach (abdominal) pain
- Headache
- Sores in or around your mouth (stomatitis)
- Indigestion (dyspepsia)
- Severe nosebleeds (epistaxis)
- Rash
- Dry eye, which may cause reduced vision
- Dizziness
- Abnormal liver enzyme results (increase in alanine aminotransferase)
- Decrease in the number of platelets (thrombocytopenia)
- Low potassium in the blood (hypokalemia)
- Abnormal liver enzyme results (increase in aspartate aminotransferase)

These are not all the possible side effects you may feel when taking ENHERTU. If you experience any side effects not listed here, contact your healthcare professional.

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| VERY COMMON Lung problems (interstitial lung disease/ pneumonitis): Cough, shortness of breath, fever, or other new or worsening breathing problems as these may be symptoms of a lung problem. | | √ | |
| Decrease in the number of white blood cells (leukocytes, lymphocytes, or neutrophils): | | √ | |

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| Fever or infection. Fatigue. Aches and pains. Flu-like symptoms. | | | |
| Decrease in the number of red blood cells (anemia): Fatigue, pale skin, shortness of breath, weakness | | √ | |
| Infections of the upper respiratory tract | | √ | |
| Difficulty breathing (dyspnea) | | √ | |
| COMMON Fever along with a decrease in the number of neutrophils (febrile neutropenia) | | √ | |
| Reactions related to the infusion of the medicine. Symptoms within 24 hours of infusion: chills or shaking, shortness of breath or wheezing, itching, rash or hives, flushing, dizziness, fever, feeling like passing out | | √ | |
| New onset or worsening shortness of breath, cough, fatigue, swelling of your ankles or legs, irregular heartbeat, sudden weight gain, dizziness, or loss of consciousness as these may be symptoms of a heart problem (decreased ejection fraction) | | √ | |
| UNCOMMON Serious complication of infection (sepsis) | | √ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mpps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ENHERTU will be stored by the healthcare professionals at the hospital or clinic where you receive treatment.

If you want more information about ENHERTU:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to date version can be found at astrazeneca.ca.

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