DOSING AND ADMINISTRATION HANDBOOK FOR YOUR PATIENTS WITH BREAST CANCER RECEIVING ENHERTU

ENHERTU (trastuzumab deruxtecan) as monotherapy, indicated for:

- the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH–) breast cancer who have received at least one prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should have received at least one and be no longer considered eligible for endocrine therapy,
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received at least one prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy, and
- the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1),

have been issued market authorization without conditions.

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; T-DM1=trastuzumab emtansine.

AstraZeneca Daiichi-Sankyo

Pr ENHERTU® trastuzumab deruxtecan

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Dosing considerations for your patients with breast cancer receiving ENHERTU[1]

ENHERTU should only be used in:

- patients with documented HER2-positive tumour status.

- patients with documented HER2-low (IHC 1+ or IHC 2+ and ISH–) tumour status based on validated assays.

Premedication

ENHERTU is emetogenic, 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 per institutional guidelines.

Recommended dose[1]

The recommended dose of ENHERTU is 5.4 mg/kg given as an IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.[1]

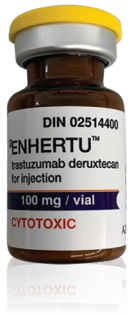
Do not substitute ENHERTU for or with trastuzumab or trastuzumab emtansine.[1]

- If infusion-related symptoms develop, the infusion rate should be slowed or interrupted.
- ENHERTU should be permanently discontinued in case of severe infusion reactions.†
- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation. Please consult Table 1 and Table 2 in the ENHERTU Product Monograph for more details.
- ENHERTU dose should not be re-escalated after a dose reduction is made.

Composition and strengths:[1]

- 100 mg vial of ENHERTU (white to yellowish-white lyophilized powder) for reconstitution and further dilution.

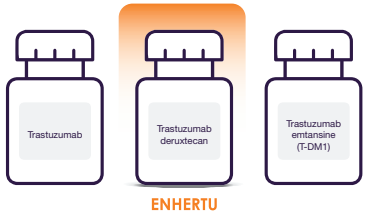
Please consult the ENHERTU Product Monograph for more details on dosing, administration and dose modification following adverse reactions.[1]



5-HT3=5-hydroxytryptamine 3; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=*in situ* hybridization; IV=intravenous; NK1=neurokinin 1.

† Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity, were reported in ENHERTU clinical trials. ENHERTU has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies. Patients should be monitored for IRRs and dose interruption or discontinuation of ENHERTU may be required based on IRR severity.[1]

Preparation for administration[1]



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).

- ENHERTU is a cytotoxic drug. Use appropriate procedures for the storage, preparation, administration, and disposal of chemotherapeutic medicinal products.
- Use appropriate aseptic techniques for reconstitution and dilution procedures.

Reconstitution[1]

- 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.

Instructions for dilution[1]

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

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

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

QUICK TIP: Diluting ENHERTU for 5.4 mg/kg dose:

Multiply patient weight (kg) by 0.27 to determine volume of reconstituted ENHERTU that needs to be further diluted.

Quick guide to determining number of vials needed to dilute ENHERTU for 5.4 mg/kg dose

Patient weight (kg)	50	60	70	80	90	100	110	120	130	140	150
Volume of reconstituted ENHERTU (mL)	13.5	16.2	18.9	21.6	24.3	27	29.7	32.4	35.1	37.8	40.5
Vials needed	 **x 3**	 **x 4**	 **x 4**	 **x 5**	 **x 5**	 **x 6**	 **x 6**	 **x 7**	 **x 8**	 **x 8**	 **x 9**

Administration[1]

Do not replace ENHERTU 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.

- ENHERTU is for intravenous use. It must be reconstituted and diluted by a healthcare professional and administered as an intravenous infusion.
- 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.[1]
- 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.
- Do not mix ENHERTU with other medicinal products or administer other medicinal products through the same intravenous line.

Missed dose

If a planned dose is delayed or missed:[1]

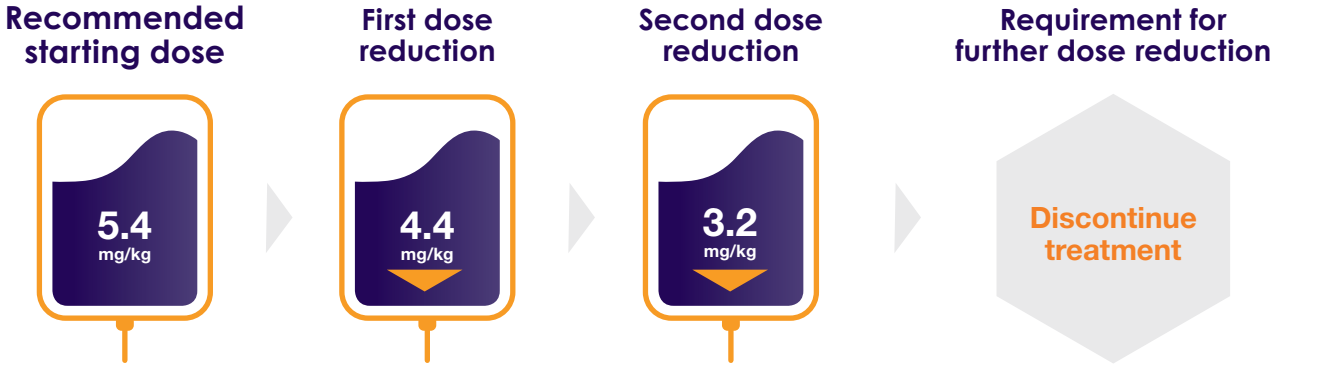
- ENHERTU should be administered as soon as possible without waiting until the next planned cycle.
- Adjust the schedule of administration to maintain a 3-week interval between doses.
- Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.

Dose modifications[1]

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of ENHERTU (see table below as well as pages 12 and 13).

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

Dose reduction schedule for patients with breast cancer



Adapted from the ENHERTU Product Monograph[1]

Please consult the ENHERTU Product Monograph for more details on dosing, administration and dose modification following adverse reactions.[1]

Recommended dose modifications for ENHERTU following adverse events[1]

Interstitial lung disease (ILD)/pneumonitis

Severity†	Treatment modification	
Asymptomatic ILD/ pneumonitis (Grade 1)	**Interrupt ENHERTU until resolved to Grade 0,** then:	
	• **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 (e.g., see page 11)**
	Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., >0.5 mg/kg/day prednisolone or equivalent).	
Symptomatic ILD/pneumonitis (Grade 2 or greater)	**Permanently discontinue ENHERTU.**	
	Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent). Continue corticosteroid treatment for at least 14 days followed by gradual taper for at least 4 weeks.	

Neutropenia

Severity†	Treatment modification	
Grade 3 (less than 1.0-0.5 x 10^9/L)	• **Interrupt ENHERTU until resolved to Grade 2 or less.**	**Maintain dose**
Grade 4 (less than 0.5 x 10^9/L)	• **Interrupt ENHERTU until resolved to Grade 2 or less.**	**Reduce dose one level (e.g., see page 11)**

Febrile neutropenia

Severity†	Treatment modification	
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.**	**Reduce dose one level (e.g., see page 11)**

Thrombocytopenia

Severity†	Treatment modification	
Grade 3 (platelets less than 50 to 25 x 10^9/L)	• **Interrupt ENHERTU until resolved to Grade 1 or less.**	**Maintain dose**
Grade 4 (platelets less than 25 x 10^9/L)	• **Interrupt ENHERTU until resolved to Grade 1 or less.**	**Reduce dose one level (e.g., see page 11)**

Decreased left ventricular ejection fraction (LVEF)

Severity†		Treatment modification	
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**. * Repeat LVEF assessment within 3 weeks.	*
	And absolute decrease from baseline is 10% to 20%	• **Interrupt ENHERTU.** * Repeat LVEF assessment within 3 weeks.	*
		• If LVEF **recovers to within 10% from baseline**.	**Resume** treatment with ENHERTU at the **same dose.**
		• If LVEF **has not recovered to within 10% from baseline**.	**Permanently discontinue ENHERTU.**
LVEF less than 40% or absolute decrease from baseline is greater than 20%		• **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)		**Permanently discontinue ENHERTU.**	

† Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

Adapted from the ENHERTU Product Monograph[1]

Cases of infusion-related reactions (IRRs), including a serious case of hypersensitivity, were reported in ENHERTU clinical trials. Patients should be monitored for IRRs and dose interruption or discontinuation of ENHERTU may be required based on IRR severity. Please refer to pages 4-5 for additional details.[1]

CHF=congestive heart failure; ILD=interstitial lung disease; IRR=infusion-related reaction; LVEF=left ventricular ejection.

ENHERTU® trastuzumab deruxtecan

Dosing and administration for patients with breast cancer treated with ENHERTU: key points[1]

- Recommended dose of ENHERTU is 5.4 mg/kg as intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity.
- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation – see Table 1 and Table 2 of the ENHERTU Product Monograph for more details.
- It is important to check the vial label to ensure that the drug being prepared and administered is ENHERTU (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine (T-DM1).
- 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 per institutional guidelines.
- Each ENHERTU vial (100 mg) should be reconstituted immediately before dilution using 5 mL of sterile water.
- If not used immediately, store the reconstituted ENHERTU vials in a refrigerator at 2°C-8°C for up to 24 hours from the time of reconstitution, protected from light. Do not freeze.
- ENHERTU should be inspected for particulates and discoloration – the solution should be clear and colorless to light yellow. Do not use if visible particles are observed or if solution is cloudy or discolored.
- ENHERTU does not contain a preservative – discard unused ENHERTU after 24 hours refrigerated.
- Dilute the calculated volume of reconstituted ENHERTU in an infusion bag containing 100 mL of 5% dextrose solution. **Do NOT use sodium chloride solution**.
- 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. Do not mix ENHERTU with other medicinal products or administer other medicinal products through the same intravenous line.
- If a dose of ENHERTU is delayed or missed, administer ENHERTU as soon as possible without waiting until the next planned cycle. Adjust the administration schedule to maintain a 3-week interval between doses.

Please consult the ENHERTU Product Monograph for more details on dosing, administration and dose modification following adverse reactions.

5-HT3=5-hydroxytryptamine 3; NK1=neurokinin 1; T-DM1=trastuzumab emtansine.

Important safety information for ENHERTU

Clinical use:

- 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.
- For pediatrics (<18 years of age), no data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Contraindications:

- Hypersensitivity to ENHERTU or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Most serious warnings and precautions:

Interstitial lung disease (ILD) and pneumonitis: Fatal cases have been reported with ENHERTU. ILD was more frequently reported in patients with moderate renal impairment in clinical trials. 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.

Embryo-fetal toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

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

Other relevant warnings and precautions:

- Left ventricular ejection fraction (LVEF) decrease
- Anemia/thrombocytopenia
- Symptomatic congestive heart failure (CHF)
- Driving and operating machinery
- Neutropenia
- Infusion-related reactions (IRR)
- Interstitial lung disease (ILD)/pneumonitis
- Race (Asian populations)
- Fertility
- Teratogenic risk
- Pregnant women or women of child-bearing potential
- Breast-feeding women

For more information:

Please consult the ENHERTU Product Monograph at enhertu-en.azpm.ca for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-668-6000.

Reference:

1. ENHERTU Product Monograph. AstraZeneca Canada Inc. January 17, 2025.

NOTES

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AstraZeneca

Daiichi-Sankyo

CA-10627E

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

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