Drug Monograph

A - Drug Name

Enhertu trastuzumab deruxtecan

COMMON TRADE NAME(S): Enhertu®

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B - Mechanism of Action and Pharmacokinetics

Enhertu® trastuzumab deruxtecan is a HER2 targeted antibody drug conjugate (ADC). It contains a humanized anti-HER2 IgG1 monoclonal antibody (trastuzumab) attached to the cytotoxic component, a topoisomerase I inhibitor (DXd), by a cleavable tetrapeptide based linker. Deruxtecan is composed of the linker and the topoisomerase I inhibitor. After binding to HER2 on cancer cells, trastuzumab deruxtecan is internalized, and the linker undergoes intracellular cleavage by lysosomal enzymes that are upregulated in tumour cells. The active topoisomerase I inhibitor that is released causes DNA damage and apoptosis.

Distribution	The C_{max} and AUC of ADC and DXd increased proportionally at various doses (3.2 - 8mg/kg). Interindividual variability is low to moderate.	
	Cross blood brain barrier?	Yes
	PPB	97% (DXd)
Metabolism	Similar to endogenous IgG, trastuzumab is expected to be degraded into small peptides and amino acids via catabolic pathways.	
	Main enzymes involved	CYP3A4 via oxidative pathways (DXd)

	Active metabolites	DXd (after intracellular cleavage by lysosomal enzymes)
	Inactive metabolites	Unknown
Elimination	Half-life	5.6 days

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C - Indications and Status

Health Canada Approvals:

- Breast Cancer
- Gastric or gastroesophageal junction (GEJ) cancer

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Non-small cell lung cancer (NSCLC)

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D - Adverse Effects

Emetogenic Potential:
High (based on Breast Advisory Committee expert opinion; a 2-3 drug antiemetic regimen is recommended in the product monograph)

Extravasation Potential: None

The following adverse effects were reported in ≥ 1% of patients with unresectable or metastatic HER2 positive breast cancer who received at least one dose of trastuzumab deruxtecan in a randomized Phase III clinical trial. Severe or life-threatening adverse events are also included from other trials.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Ejection fraction decreased (2%)	E D
Dermatological	Alopecia (37%) (<1% severe)	E D
	Rash, pruritus (8%)	E
	Skin hyperpigmentation (6%)	E D
Gastrointestinal	Abdominal pain (21%)	E
	Anorexia, weight loss (29%) (2% severe)	E
	Constipation (34%)	E
	Diarrhea (29%)	E
	Dyspepsia (11%)	E
	Mucositis (20%)	E
	Nausea, vomiting (76%) (7% severe)	E
General	Fatigue (49%)	E
Hematological	Febrile neutropenia (<1%)	E
	Myelosuppression ± infection, bleeding (43%) (19% severe)	E
Hepatobiliary	↑ LFTs (32%) (2% severe)	E
Hypersensitivity	Infusion related reaction (2%) (may be severe)	I
Metabolic / Endocrine	↓ K (13%)	E
Musculoskeletal	Musculoskeletal pain (31%) (1% severe)	E
Nervous System	Dizziness (12%)	E
	Dysgeusia (6%)	E
	Headache (22%)	E
	Peripheral neuropathy (13%)	E D
Ophthalmic	Blurred vision (4%)	E
Respiratory	Cough, dyspnea (11%)	E
	Pneumonitis (11%) (1% severe)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for Enhertu® trastuzumab deruxtecan include nausea, vomiting, fatigue, myelosuppression ± infection, bleeding, alopecia, constipation, ↑ LFTs, musculoskeletal pain, anorexia, weight loss, diarrhea and headache.

Interstitial lung disease (ILD) and **pneumonitis** have been observed. Although Grade ≥ 3 events, including fatalities, occurred during clinical trials, most cases reported were Grade ≤ 2. The median onset was ~6 months.

Decreases in **left ventricular ejection fraction (LVEF)** have occurred with trastuzumab deruxtecan. LVEF should be monitored if clinically indicated. Interruption or discontinuation of treatment may be required depending on severity (see Dose Modifications section).

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

HER2-Positive Breast, Gastric, GEJ Cancer: Use only in patients with documented HER2-positive tumour status based on validated assays.

HER2-Low Breast Cancer: Use only in patients with documented or HER2-low tumour status (immunohistochemistry [IHC] 1+ or IHC 2+ / in-situ hybridization [ISH] negative tumour status) based on validated assays.

Enhertu® trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).

Adults:

Breast cancer:

Intravenous: 5.4 mg/kg every 21 days

Gastric / GEJ Cancer:

Intravenous: 6.4 mg/kg every 21 days

Dosage with Toxicity:

Dose Level	Trastuzumab Deruxtecan Dose* (mg/kg)	
	Breast Cancer	Gastric / GEJ Cancer
0	5.4	6.4
-1	4.4	5.4
-2	3.2	4.4
-3	Discontinue	Discontinue

*****Do not re-escalate a previously reduced dose.

Dose Modification for Toxicity:

Toxicity / Grade		Action
Interstitial lung disease (ILD)/ pneumonitis	Grade 1	Hold*. Consider corticosteroid (e.g. >0.5 mg/kg/day prednisolone or equivalent). If resolved in ≤ 28 days, resume at same dose level. If resolved in > 28 days, resume at 1 dose level ↓.
	Grade ≥ 2	Discontinue permanently. Initiate corticosteroids (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.
Neutropenia	Grade 3	Hold*. Resume at same dose level.
	Grade 4	Hold*. Resume at 1 dose level ↓.
Febrile neutropenia		Hold*. Resume at 1 dose level ↓.
Thrombocytopenia	Grade 3	Hold*. Resume at same dose level.
	Grade 4	Hold*. Resume at 1 dose level ↓.

*Do not restart treatment until ILD/pneumonitis recovered to Grade 0, febrile neutropenia resolved, ANC ≥ 1 x 10^9/L, and platelets ≥ 75 x 10^9/L.

Dose Modification for Left Ventricular Ejection Fraction (LVEF) Decreased:

	LVEF		Absolute Decrease from Baseline	Action
Asymptomatic	> 45%	AND	10 - 20%	Continue dose.
	40 - 45%	AND	< 10%	Continue dose. Reassess within 3 weeks.
		AND	10 - 20%	Hold dose. Reassess within 3 weeks. If LVEF recovered to within 10% from baseline, resume at same dose level. If not recovered to within 10% from baseline, discontinue permanently.
	< 40%	OR	> 20%	Hold dose. Reassess within 3 weeks. If LVEF < 40% or absolute decrease > 20% from baseline confirmed, discontinue permanently.
Symptomatic	Any			Discontinue permanently

Management of Infusion-Related Reactions (IRRs):

Enhertu® trastuzumab deruxtecan has not been studied in patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Stop or slow the infusion rate (e.g. by 50%) if infusion reactions occur. Discontinue for severe reactions.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Dosage with Hepatic Impairment:

Bilirubin		AST	Trastuzumab Deruxtecan Dose
≤ ULN	AND	> ULN	No dose adjustment.
>1 to 1.5 x ULN	AND	any	
>1.5 to 3 x ULN	AND	any	Insufficient data. Monitor closely for toxicity.
>3 x ULN	AND	any	No data available.

Dosage with Renal Impairment:

Patients with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis.

Creatinine Clearance (mL/min)	Trastuzumab Deruxtecan Dose
≥ 60	No dose adjustment.
≥ 30 to < 60	No dose adjustment. Monitor closely for toxicity.
< 30	No data available.

Dosage in the elderly:

No dose adjustment is required in patients ≥ 65 years. No clinically relevant differences in efficacy were observed based on age. Some clinical studies suggested a difference in safety between patients ≥ 65 years compared to younger patients.

Dosage based on gender:

Gender has no significant effect on pharmacokinetic parameters of trastuzumab deruxtecan, or released topoisomerase I inhibitor, based on population pharmacokinetic analysis.

Dosage based on ethnicity:

No relevant differences in efficacy of trastuzumab deruxtecan were observed based on ethnicity.

Asian patients with gastric cancer receiving trastuzumab deruxtecan had a higher incidence of hematologic adverse events compared to non-Asian patients.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

Enhertu® trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, or Kadcyla® trastuzumab emtansine).

- Reconstitute each vial with sterile water for injection to a final concentration of 20 mg/mL and gently swirl. Do not shake the solution.
- Further dilute in 100 mL of D5W. Do NOT use sodium chloride solution.
- A polyvinylchloride (PVC) or polyolefin infusion bag is recommended. Invert infusion bag gently to mix.
- Administer as an IV infusion only with a 0.20 or 0.22 micron in line polyethersulfone (PES) or polysulfone (PS) filter. Do NOT administer as an IV push or bolus.
- Do not admix with other drugs or administer other drugs through the same IV line.
- Administer the first infusion over 90 minutes. If well tolerated, may give subsequent infusions IV over 30 minutes.
- If the diluted solution was stored refrigerated (2°C to 8°C), allow solution to reach room temperature before administration.
- If a planned dose is missed, administer as soon as possible. Adjust the schedule to maintain a 3-week interval between doses.
- Cover reconstituted drug and diluted solution to **protect from light** during storage and administration.
- Store unopened vials in a refrigerator at 2-8^{o}C in the original carton. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to this drug or any components of its components.

Other Warnings/Precautions:

- Enhertu® trastuzumab deruxtecan is **not interchangeable** with other trastuzumab products (e.g. Herceptin®, trastuzumab biosimilars, Kadcyla® trastuzumab emtansine).
- Trastuzumab deruxtecan has not been studied in patients with a history of clinically significant cardiac disease, baseline LVEF < 50% or severe hypersensitivity reactions to other monoclonal antibodies.
- Patients with a previous history of ILD/pneumonitis or with moderate or severe renal impairment may be at a higher risk of developing ILD/pneumonitis.
- Patients should use caution when driving, operating machinery or performing tasks that require alertness if they experience headache and dizziness.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: No
- Genotoxicity: Yes
- Embryotoxicity: Yes
- Teratogenicity: Yes
- Pregnancy:
  Enhertu® trastuzumab deruxtecan is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **7 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **4 months** after the last dose.
- Excretion into breast milk: Likely
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **7 months** after the last dose.
- Fertility effects: Probable
  - Documented in studies with male animals.
  - Discuss fertility preservation especially with male patients prior to starting treatment.
  - Patients should not donate sperm during treatment and for at least 4 months after the last dose

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H - Interactions

DXd is a substrate of P-gp, OATP1B1, OATP1B3, MATE2-K, MRP1, and BCRP.

No dose adjustment is required during coadministration with drugs that are inhibitors of OATP1B or CYP3A.

No clinically significant interactions are expected with inhibitors of P-gp, MATE2-K, MRP1, or BCRP transporters.

DXd does not inhibit or induce major CYP450 enzymes.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each dose and as clinically indicated
LVEF	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, fatigue, hypersensitivity or infusion reactions, GI, respiratory and dermatological effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Trastuzumab Deruxtecan - Unresectable Locally Advanced or Metastatic Breast Cancer
- Trastuzumab Deruxtecan - HER2-low Unresectable Locally Advanced or Metastatic Breast Cancer
- Trastuzumab Deruxtecan - Previously Treated Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

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K - References

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Corti C, Antonarelli G, Criscitiello C, Lin NU, Carey LA, Cortés J, Poortmans P, Curigliano G. Targeting brain metastases in breast cancer. Cancer Treat Rev. 2022 Feb;103:102324. doi: 10.1016/j.ctrv.2021.102324. Epub 2021 Dec 16. PMID: 34953200.

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Antiemesis. Version 2.2022, March 23, 2022.

Prescribing Information: Enhertu® (trastuzumab deruxtecan). Daiichi Sankyo Inc and AstraZeneca Pharmaceuticals LP, May 2022.

Product Monograph: Enhertu® (trastuzumab deruxtecan). AstraZeneca Canada Inc, January 17, 2025.

Trastuzumab deruxtecan (interim monograph). BC Cancer Drug Manual. December 1, 2021.

May 2025 Updated Indications, Adverse effects, Dosing, and Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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