DRUG NAME: Trastuzumab deruxtecan

SYNONYM(S):

COMMON TRADE NAME(S): ENHERTU®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Trastuzumab deruxtecan is a HER2 targeted antibody drug conjugate composed of a humanized anti-HER2 IgG1 antibody (trastuzumab) connected to a topoisomerase I inhibitor by a cleavable tetrapeptide-based linker. Following binding to HER2 on the tumour cell, trastuzumab deruxtecan is internalized and the linker is cleaved by lysosomal enzymes that are upregulated in cancer cells. Upon release from the conjugate, the topoisomerase I inhibitor component causes DNA damage and apoptotic cell death of the tumour cell.[1]

USES:

Primary uses:

*Breast cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to trastuzumab, trastuzumab emtansine, or Chinese hamster ovary cell proteins[1,2]

Caution:

- trastuzumab deruxtecan (ENHERTU®) is ***NOT interchangeable*** with trastuzumab (HERCEPTIN®) or trastuzumab emtansine (KADCYLA®) and should not be substituted[1]
- patients with moderate or severe ***renal or hepatic impairment*** may experience a higher incidence of adverse events[1]
- ***left ventricular ejection fraction (LVEF)*** decrease has been observed with trastuzumab deruxtecan treatment; monitor LVEF as clinically indicated[1]

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SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (34-72%, severe 8-9%)
	febrile neutropenia (2%)
	leukopenia (21-72%, severe 6-9%)
	lymphopenia (11%, severe 5%)
	neutropenia (33-65%, severe 18-19%); may require dose interruption and/or reduction
	thrombocytopenia (23-43%, severe 4%)
cardiac	***left ventricular dysfunction*** (1%, severe <1%); see paragraph following **Side Effects** table
eye	dry eye (12%, severe <1%)
gastrointestinal	*emetogenic potential:* moderate[3]
	abdominal pain (20%, severe 1%)
	constipation (36%, severe 1%)
	diarrhea (31%, severe 3%)
	dyspepsia (14%)
	nausea (80%, severe 7%)
	stomatitis (15%, severe 1%)
	vomiting (49%, severe 4%)
general disorders and administration site conditions	*extravasation hazard:* none[4]
	fatigue (60%, severe 6%)
immune system	***infusion related reactions*** (3%)
infections and infestations	sepsis (1%)
	upper respiratory tract infection (18%, severe 6%)
investigations	ALT increase (11-41%, severe 1%)
	AST increase (15-44%, severe 1%)
	hypokalemia (13-28%, severe 3-4%)
metabolism and nutrition	appetite decrease (35%, severe 1%)
nervous system	dizziness (11%)
	headache (20%)
respiratory, thoracic and mediastinal	cough (21%)
	dyspnea (15%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	epistaxis (14%)
	interstitial lung disease/pneumonitis (14%, severe 3%); see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (46%, severe <1%)
	rash (13%, severe <1%)

Adapted from standard reference[1] unless specified otherwise.

Left ventricular ejection fraction (LVEF) decrease has been observed with trastuzumab deruxtecan. Some patients may be asymptomatic or present with abnormal laboratory findings only. If clinically indicated, monitor LVEF prior to treatment and then as required thereafter. If LVEF falls below 40% or the absolute decrease from LVEF baseline is greater than 20% and LVEF does not recover after a 3 week dose interruption, trastuzumab deruxtecan should be permanently discontinued. Permanently discontinue trastuzumab deruxtecan in patients with symptomatic congestive heart failure.[1]

Interstitial lung disease and/or ***pneumonitis*** have been reported with trastuzumab deruxtecan. Most events are grade 1 or 2, but grade 3 events and fatalities have been reported. Patients with a history of ILD may be at increased risk of developing ILD with trastuzumab deruxtecan. Median time to onset is 4.4 months (range 1-11 months). Monitor for symptoms of cough, dyspnea, fever, and/or new or worsening respiratory symptoms. Evaluate suspected ILD by radiographic imaging. ILD is managed with systemic corticosteroids and withholding trastuzumab deruxtecan until complete resolution of clinical symptoms and CT findings. Permanently discontinue trastuzumab deruxtecan for confirmed symptomatic grade 2 or greater ILD.[1]

INTERACTIONS: none known[1]

SUPPLY AND STORAGE:

Injection: AstraZeneca Canada Inc. supplies trastuzumab deruxtecan as 100 mg preservative free vials of lyophilized powder. Refrigerate. Store in original carton to protect from light.[5]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

- do NOT use sodium chloride solution for reconstitution or dilution[1]
- if the compounded preparation is stored in the fridge prior to administration, allow infusion bag to equilibrate to room temperature before administering[1]
- product must be protected from light during all steps of preparation and infusion bag must be covered for administration and storage[6]

Compatibility: consult detailed reference

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PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[1]	do NOT use
Intermittent infusion[1]	***over 90 min,*** using a ***0.2 or 0.22 micron in-line filter;*** if well tolerated, subsequent infusions can be given ***over 30 min***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	3 weeks[1]:	5.4 mg/kg IV for one dose on day 1 (total dose per cycle 5.4 mg/kg [range 3.2-5.4 mg/kg]) Dose should not be re-escalated after dose reduction.[1]

REFERENCES:

1. AstraZeneca Canada Inc. ENHERTU® product monograph. Mississauga, Ontario; 15 April 2021
2. BC Cancer. Cancer Drug Manual® Trastuzumab monograph. Vancouver, British Columbia: BC Cancer; 1 January 2013
3. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
4. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; 1 March 2021
5. AstraZeneca Canada Inc. ENHERTU® product monograph. Mississauga, Ontario; November 19, 2021
6. AstraZeneca Canada Inc. Medical Information. 5 October2021

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