DRUG NAME: Trastuzumab deruxtecan

SYNONYM(S): T-DXd, DS-8201a, Fam-trastuzumab deruxtecan-nxki[1]

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 directed antibody-drug conjugate (ADC). The humanized IgG1 monoclonal antibody (trastuzumab) is linked to DXd (topoisomerase I inhibitor) by a tetrapeptide-based cleavable linker. Following binding to HER2 receptors on tumour cells, trastuzumab deruxtecan is internalized and DXd is released intracellularly. DXd prevents re-ligation of the DNA strand, resulting in DNA damage, apoptosis, and cell death.[2,3] Trastuzumab deruxtecan has a high drug to antibody ratio (i.e., approximately 8 molecules of DXd for each antibody molecule) which enables effective delivery of DXd into tumour cells and activity against low HER2-expressing tumours. Furthermore, DXd also can penetrate into the microenvironment and neighboring tumour cells resulting in a potent bystander effect upon release within the target cells. DXd is cell cycle phase-specific and stalls cell cycle progression at S phase.[4-6]

PHARMACOKINETICS:

Absorption	trastuzumab deruxtecan: Tmax = 2.2 h DXd: Tmax = 6.8 h	
Distribution	trastuzumab deruxtecan is primarily limited to vascular space; minimal tissue distribution in animal studies[7]	
	cross blood brain barrier?	yes[8]
	volume of distribution	trastuzumab deruxtecan: 2.7-3.7 L
	plasma protein binding	DXd: 97%
Metabolism	trastuzumab: expected to undergo catabolism to small peptides and amino acids DXd: primarily via oxidation by CYP3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily by biliary elimination	
	urine	as unchanged DXd
	feces	major excretion pathway; as unchanged DXd
	terminal half life	trastuzumab deruxtecan: 5.6 days DXd: 5.6 days
	clearance	trastuzumab deruxtecan: 0.4 L/day DXd: 18.3 L/h
Sex	no clinically meaningful difference	
Elderly	no clinically meaningful difference	
Ethnicity	no clinically meaningful difference	

Adapted from standard reference[2,3] unless specified otherwise.

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USES:

Primary uses:
*Breast cancer

Other uses:
Lung cancer, non-small cell[3]
Gastric cancer[3]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to trastuzumab, trastuzumab emtansine, or Chinese hamster ovary cell proteins[9,10]

Caution:
- trastuzumab deruxtecan (ENHERTU®) is ***NOT interchangeable*** with trastuzumab (HERCEPTIN®) or trastuzumab emtansine (KADCYLA®) and should not be substituted[2]
- ***left ventricular dysfunction*** has been reported; caution in patients with history of clinically significant cardiac disease or left ventricular ejection fraction (LVEF) less than 50% prior to the treatment[2]
- patients with a history of ***interstitial lung disease (ILD)/pneumonitis*** or moderate to severe ***renal impairment*** are at increased risk of ILD/pneumonitis[2]

Carcinogenicity: No carcinogenicity studies for trastuzumab deruxtecan have been conducted.[2]

Mutagenicity: DXd (topoisomerase inhibitor component of trastuzumab deruxtecan) was not mutagenic in Ames test. DXd was clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: In animal studies, spermatid retention and decreased round spermatids were observed at exposures approximately 4-9 times those seen following human clinical exposure. Testicular changes (tubular degeneration/atrophy and decreased testicular/epididymal weights) and reduced sperm count were observed at exposures approximately 19 times those seen following human clinical exposure. Based on animal findings, trastuzumab deruxtecan may impair male reproductive function and fertility. Consider sperm banking prior to treatment if applicable and avoid sperm donation throughout treatment and for at least 4 months after the final dose of trastuzumab deruxtecan.[2,3]

Pregnancy: Based on its mechanism of action, trastuzumab deruxtecan is expected to cause teratogenicity and embryotoxicity in humans. In animal studies, trastuzumab deruxtecan and DXd were toxic to rapidly dividing cells and DXd was also genotoxic. There is no data in pregnant women. In post marketing reports, oligohydramnios, fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with trastuzumab. For females of reproductive potential, contraception is recommended during treatment with trastuzumab deruxtecan and for at least 7 months after the last dose. For males with female partners of reproductive potential, contraception is recommended during treatment and for at least 4 months after the last dose.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Because trastuzumab is a humanized IgG1 and human IgG is known to be excreted in human milk, breastfeeding should be avoided during treatment and for at least 7 months after the final dose of trastuzumab deruxtecan.[2]

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.[11,12]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (31-39%, severe 8-10%)
	disseminated intravascular coagulation (severe 1%); fatalities reported[3]
	febrile neutropenia (1%, severe 1%); fatalities reported
	leukopenia (21-31%, severe 7%)
	lymphopenia (11%, severe 4-6%)
	neutropenia (33-43%, severe 19%)
	thrombocytopenia (26%, severe 4-7%)
cardiac	acute myocarditis[3,13]
	left ventricular dysfunction; see paragraph following **Side Effects** table
eye	dry eye (12%, severe 1%)
	blurred vision (5%)
gastrointestinal	*emetogenic potential:* high[14,15]
	abdominal pain (21%, severe 1%)
	abdominal distension (5%)
	constipation (34%, severe 1%)
	diarrhea (30%, severe 1-3%)
	dyspepsia (11-14%)
	flatulence (2%)
	gastritis (3%, severe 1%)
	nausea (76-80%, severe 7%)
	stomatitis (15-20%, severe 1%)
	vomiting (49%, severe 2-4%)
general disorders and administration site conditions	*extravasation hazard:* none[16]
	fatigue (49-60%, severe 6-9%)
	peripheral edema (10%)[5]
	pyrexia (12%, severe 1%)
hepatobiliary	cholestatic jaundice[3]
infections and infestations	sepsis (1%); fatalities reported
	pneumonia; fatalities reported
	respiratory tract infection (14-22%, severe 6%)
injury, poisoning, and procedural complications	***infusion-related reactions*** (1-3%)
investigations	albumin decrease (39%)[5]
	alkaline phosphatase increase (14-49%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ALT increase (11-53%, severe 1%)
	AST increase (15-67%, severe 1%)
	bilirubin increase (16-20%, severe 1%)
	creatinine increase (16%, severe 1%)
	left ventricular ejection fraction (LVEF) decrease (2-8%, severe 1%)[3]; see paragraph following **Side Effects** table
	weight loss (17%, severe 1%)
metabolism and nutrition	appetite decrease (30-35%, severe 2%)
	dehydration (2-4%, severe 1%)
	hypokalemia (13-35%, severe 4%)
	hypomagnesemia (1-10%)[5]
musculoskeletal and connective tissue	musculoskeletal pain (31%, severe 1%)
nervous system	dizziness (10-13%, severe 1%)
	headache (15-22%, severe 1%)
	peripheral neuropathy (13%, severe 1%)
	dysgeusia (6-10%, severe 1%)
respiratory, thoracic and mediastinal	***cough*** (10-21%, severe 1%)
	dyspnea (8-15%, severe 2%); fatalities reported
	epistaxis (11-14%)
	interstitial lung disease (ILD)/pneumonitis (9-14%, severe 1-3%); see paragraph following **Side Effects** table
	respiratory failure
skin and subcutaneous tissue	alopecia (37-46%, severe 1%)
	pruritus (3-8%, severe 1%)
	rash (8-13%, severe <1%)
	skin hyperpigmentation (3-6%)
vascular	hemorrhage (16%)[3]; includes tumour hemorrhage and hemorrhage at various sites

Adapted from standard reference[2,3] unless specified otherwise.

Fatal ***interstitial lung disease (ILD)*** and ***pneumonitis*** have been reported. The incidence of ILD is higher in patients with moderate renal impairment (CrCl 30 to 60 mL/min) compared to patients with mild renal impairment (CrCl 60 to 90 mL/min). Median time to onset is 5 months. Advise patients to promptly report cough, dyspnea, fever, or any new/worsening respiratory symptoms. For grade 1 events (i.e., asymptomatic ILD/pneumonitis), management may include dose interruption, corticosteroid, and dose reduction. Dose should not be re-escalated after dose reduction. For grade 2 or greater events, permanently discontinue trastuzumab deruxtecan and promptly initiate corticosteroid.[2]

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Left ventricular dysfunction has been observed with trastuzumab deruxtecan. Monitor LVEF prior to and during treatment if clinically indicated. Management may include dose interruption, re-assessment, and/or discontinuation of trastuzumab deruxtecan, depending on the severity and recovery. Permanently discontinue if LVEF less than 40% or an absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue trastuzumab deruxtecan in patients with symptomatic congestive heart failure.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
itraconazole[2,5]	no clinically meaningful increase in Cmax and AUC of trastuzumab deruxtecan	strong inhibition of CYP 3A4 by itraconazole	no dose adjustment required
ritonavir[2,5]	no clinically meaningful increase in Cmax and AUC of trastuzumab deruxtecan	combined inhibition of OATP1B and CYP 3A4 and by ritonavir	no dose adjustment required

In vitro, trastuzumab deruxtecan is a substrate of BCRP, MATE2-K, MRP1 and P-gp; clinical significance is unknown.[2,3]

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.[2]

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[2]
- product must be protected from light during all steps of preparation and infusion bag must be covered for storage and administration[2]
- if the compounded preparation is stored in the fridge prior to administration, allow infusion bag to equilibrate to room temperature before administering[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[2]	do NOT use

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

Intermittent infusion[2,17]	***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***

Intravenous:

Cycle Length:

3 weeks[2,17]: ***5.4 mg/kg*** (range 3.2-5.4 mg/kg) IV ***for one dose on day 1***
(total dose per cycle 5.4 mg/kg [range 3.2-5.4 mg/kg])

3 weeks[3]: 6.4 mg/kg (range 4.4-6.4 mg/kg) IV for one dose on day 1
(total dose per cycle 6.4 mg/kg [range 4.4-6.4 mg/kg])

Doses should not be re-escalated after dose reduction.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure[2]*:*

CrCl ≥60 mL/min: no adjustment required
CrCl 30-60 mL/min: no adjustment required; monitor for toxicity
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[2,3]*:*

mild impairment (total bilirubin >1-1.5xULN): no adjustment required
moderate impairment (total bilirubin ≥1.5-3xULN): no adjustment required; monitor for toxicity due to potential increased exposure to DXd
severe impairment (total bilirubin >3xULN): no information found; monitor for toxicity due to potential increased exposure to DXd

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

Dosage in dialysis: no information found

Children: safety and efficacy not established

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