

## DRUG NAME: Datopotamab deruxtecan

**SYNONYM(S):** Dato-DXd<sup>1</sup>, DS-1062a<sup>1</sup>

**COMMON TRADE NAME(S):**

**CLASSIFICATION:** miscellaneous

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

### MECHANISM OF ACTION:

Datopotamab deruxtecan is an antibody-drug conjugate comprised of a recombinant human anti-trophoblast cell surface antigen 2 (TROP2) IgG1 monoclonal antibody (MAAP-9001a) bound to a topoisomerase I inhibitor (DXd) via a covalently conjugated cleavable drug linker. TROP2 is a trophoblast cell surface antigen involved in calcium signal and the protein is produced by the TACSTD2 gene. It is a transmembrane glycoprotein involved in many cell signaling pathways and is often upregulated in cancer cells. Datopotamab deruxtecan binds to TROP2 on the cell surface of a TROP2 expressing cell and is internalized. After enzymatic processing in the cell, the cytotoxic payload (DXd) is released into the cytoplasm, where it inhibits cell replication by causing double-stranded DNA breaks and promotes cell apoptosis of the target cell.<sup>1,2</sup>

### USES:

**Primary uses:**

**Other uses<sup>1</sup>:**

Breast cancer  
Lung cancer, non-small cell  
Lung cancer, small cell

\*Health Canada approved indication

### SPECIAL PRECAUTIONS:

**Caution:**

- to prevent **infusion related reactions**, premedication with antihistamine and acetaminophen is required before every dose of datopotamab deruxtecan; premedication with glucocorticoids is optional<sup>3</sup>

**Carcinogenicity:** The possibility of genotoxicity leading to a secondary malignancy cannot be ruled out because plasma exposure levels of DXd in humans at clinical doses would be higher than exposure levels causing chromosomal aberration in nonclinical studies.<sup>1</sup>

**Mutagenicity:** Not mutagenic in bacterial mutation test. Datopotamab deruxtecan is genotoxic in mammalian *in vitro* and *in vivo* chromosome tests.<sup>1</sup>

**Fertility:** In animal studies, effects on the male reproductive system included degeneration of the germinal epithelium, atrophy of the seminiferous tubules, cell debris, reduction in the number of spermatozoa in the ducts, and single cell necrosis of the ductal epithelium in the epididymis. In female test subjects, an increased number of atretic follicles in the ovary and single cell necrosis of the mucosal epithelium in the vagina was observed.<sup>1</sup>

**Pregnancy:** TROP2 plays a critical role in development of embryony, formation of placenta and proliferation of stem cells with a regulatory role in cell-cell adhesion. Datopotamab deruxtecan inhibits TROP2. DXd (the cytotoxic payload of datopotamab deruxtecan) is toxic to rapidly dividing cells and is genotoxic. Based on the known

mechanism of action of DXd, datopotamab deruxtecan may cause fetal harm if administered during pregnancy. Any potential embryo-fetal toxicity is expected to be serious.<sup>1,2</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk.

**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  $\geq 5\%$  higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
blood and lymphatic system/ febrile neutropenia	<b><i>anemia</i></b> (20-35%, severe 3-6%)
	leukopenia (11-20%, severe 2-3%)
	lymphocytopenia (severe 4-11%)
	lymphopenia (severe 4%)
	<b><i>neutropenia</i></b> (14-25%, severe 3-9%)
eye	dry eye (14-20%)
	<b><i>keratitis</i></b> (severe <1%); see paragraph following <b>Side Effects</b> table
gastrointestinal	<i>emetogenic potential: low</i> <sup>4,5</sup>
	abdominal pain (severe 2%)
	constipation (20-32%)
	diarrhea (15%)
	<b><i>nausea</i></b> (32-61%)
	<b><i>stomatitis</i></b> (28-78%, severe 3-11%); see paragraph following <b>Side Effects</b> table
	vomiting (14-32%, severe 2%)
general disorders and administration site conditions	<i>extravasation hazard: none</i> <sup>6</sup>
	extravasation (<1%)
	<b><i>fatigue, asthenia</i></b> (11-40%, severe 2-5%)
infections and infestations	COVID 19 (16%)
	pneumonia (severe 5-6%)
injury, poisoning, and procedural complications	<b><i>infusion-related reactions</i></b> (12%, severe <1%); includes anaphylaxis
investigations	amylase increase (severe 2-6%)
	AST/ALT increase (12-22%, severe 2%)
	bilirubin increase (severe 4%)
	creatinine phosphokinase increase (severe 2%)
	hypocalcemia (severe 2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
	hypokalemia (severe 4%)
	hyponatremia (severe 2%)
metabolism and nutrition	appetite decrease (11-29%, severe 3%)
nervous system	headache (27%)
respiratory, thoracic and mediastinal	cough (12%)
	dyspnea (severe 2%)
	<b>interstitial lung disease/pneumonitis</b> (4-6%, severe <3%); see paragraph following <b>Side Effects</b> table
skin and subcutaneous tissue	<b>alopecia</b> (20-51%)
	dry skin (7%)
	eye brow, eye lash hair loss (1%)
	hyperpigmentation (5%)
	pruritus (7%, severe <1%)
	<b>rash</b> (16%, severe <1%)

Adapted from standard reference<sup>1</sup> unless specified otherwise.

**Infusion related reactions** may include fever/chills with or without nausea/vomiting, pain, headache, dizziness, dyspnea, and hypotension. To prevent reactions, including anaphylaxis, premedication with antihistamines and acetaminophen (plus/minus glucocorticoids) should be given with each dose of datopotamab deruxtecan. Reactions occurring during the infusion are managed with infusion rate reduction, dose interruption, or permanent discontinuation depending on their severity. Following a grade 1 or 2 reaction, subsequent infusions should be initiated at a reduced rate. If no reaction is observed, the initial planned rate may be resumed. Discontinue datopotamab deruxtecan for grade 3 or 4 reactions.<sup>3</sup>

**Interstitial lung disease (ILD)/pneumonitis** is considered an identified risk of treatment with datopotamab deruxtecan based on available nonclinical and clinical data and review of in-class drugs. Monitor patients for signs/symptoms of ILD, including cough, fever, and dyspnea and proactively manage using dose modifications (e.g., delay, dose reduction). Prompt use of steroids is considered key in reducing serious adverse outcomes.<sup>1</sup>

**Keratitis** is considered an identified risk of treatment with datopotamab deruxtecan based on the potential for serious consequences if left unmanaged. **Corneal toxicity** was observed in nonclinical studies and has been associated with drugs of a similar class. The mechanism and relationship of corneal toxicity to datopotamab deruxtecan is unclear; however, punctate and ulcerative keratitis have been reported. Suggested preventative measures include artificial tears (preferably preservative free) given 4 times daily and avoidance of contact lenses. Monitor patients for signs/symptoms of keratitis, including dry eye, increased lacrimation, photophobia, and vision changes and proactively manage using dose modifications. Artificial tears can be increased up to 8 times daily to manage symptoms if clinically indicated. Ophthalmologist consultation may be required.<sup>1</sup>

Oral **mucositis/stomatitis** can include erythema, ulceration, mouth/throat pain, and bleeding of the oral mucosa. Other signs and symptoms may include dry mouth, thickening of the saliva, increased mucous production, red/shiny/swollen gums, soft white patches or pus on the tongue, and trouble swallowing or talking. Adherence to good oral hygiene is recommended and includes gentle brushing/flossing of teeth and daily use of a steroid containing mouthwash (or other bland/inert mouthwash). Prophylactic cryotherapy (i.e., ice chips or ice water held in the mouth during infusion) can be considered.<sup>7</sup>

## INTERACTIONS:

Formal drug interaction studies with datopotamab deruxtecan have not been done and the risk in humans has not been assessed. Based on *in vitro* human studies, DXd is a substrate for CYP 3A4 and the following transporters: P-gp, MATE2-K, OATP1B1, OATP1B3, BCRP, and MRP1. Caution is suggested when datopotamab deruxtecan is used concurrently with strong inhibitors of CYP3A4 and dual inhibitors of OATP1B/CYP 3A as modelling suggests the AUC of datopotamab deruxtecan may be increased. Monitor for toxicity.<sup>1</sup>

DXd is an inhibitor of OAT1 and OATP1B1 *in vitro*; however data suggests that datopotamab deruxtecan at clinical doses will have no effect on the pharmacokinetics of substrates of these transporters.<sup>1</sup>

## SUPPLY AND STORAGE:

**Injection:** Daiichi Sankyo and AstraZeneca supply datopotamab deruxtecan as 100 mg single-use (preservative free) vials of lyophilized powder. Refrigerate. Protect from light.<sup>8</sup>

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; datopotamab deruxtecan is not compatible with saline<sup>8</sup>
- administer using a 0.2 or 0.22 micron filter<sup>8</sup>
- protect prepared IV bag from light after preparation<sup>8</sup> (e.g., cover with amber bag)
- if the compounded preparation is stored in the fridge prior to use, allow infusion bag to equilibrate to room temperature before administering<sup>8</sup>

**Compatibility:** consult detailed reference

## PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
<b><i>Intermittent infusion</i></b>	<b><i>over 90 min</i></b> <sup>5</sup> ; administer using a 0.2 or 0.22 micron in-line filter <sup>8</sup>
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:	
<i>Intravenous:</i>	<b>3 weeks<sup>5</sup>:</b>	<b>6 mg/kg</b> (range 2-6 mg/kg) <b><i>IV for one dose on day 1</i></b> (total dose per cycle 6 mg/kg [range 2-6 mg/kg])

## REFERENCES:

1. Daiichi Sankyo and AstraZeneca. DS-1062a (Dato-DXd) Investigator's Brochure - Edition 8.0. Tokyo, Japan; May 7, 2024.
2. Gadaleta-Caldarola G, Lanotte L, Infusino S, et al. Safety evaluation of datopotamab deruxtecan for triple-negative breast cancer: a meta-analysis. *Cancer Treat Res Commun* ; 2023;37:100775
3. Daiichi Sankyo and AstraZeneca. Toxicity Management Guidelines: DS-1062a (Dato-DXd). Tokyo, Japan; February 16, 2024.
4. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1, 2022.
5. Bionical Emas for Daiichi Sankyo. Dato-DXd – Frequently Asked Questions. Version 3.0. Wellington, Derbyshire, England;
6. 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; March 1, 2021.
7. Daiichi Sankyo Inc. Clinical Study Site Pocket Guide: Datopotamab Deruxtecan (Dato-DXd). Tokyo, Japan; June, 2024.
8. Daiichi Sankyo Inc. Dose Preparation Instructions: DS-1062a for Injection 100 mg (Lyophilized Powder). Version 4. Tokyo, Japan; September 10, 2022.