DRUG NAME: Trastuzumab emtansine

SYNONYM(S): T-DM1, trastuzumab-DM1, trastuzumab-MCC-DM1, ado-trastuzumab emtansine[1]

COMMON TRADE NAME(S): KADCYLA®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Trastuzumab emtansine is an antibody-drug conjugate incorporating the monoclonal antibody trastuzumab and emtansine. The emtansine moiety is comprised of two components, DM1, a microtubule inhibitor, and MCC, a thioether linker. Trastuzumab emtansine binds to human epidermal growth factor 2 (HER2) receptors and undergoes internalization and lysosomal degradation, resulting in increased targeted delivery of DM1 to malignant cells that overexpress HER2. The trastuzumab moiety binds to HER2 receptors on the tumour surface and inhibits shedding of the HER2 extracellular domain, inhibits HER2 signaling, and mediates antibody-dependent cell-mediated cytotoxicity. Once internalized, the emtansine moiety binds to tubulin, resulting in cell cycle arrest in the G2/M phase and apoptosis.[2]

PHARMACOKINETICS:

Distribution	systemic accumulation is not observed with repeat doses[1]	
	cross blood brain barrier?	no information found
	volume of distribution[3]	3.13 L
	plasma protein binding[1]	DM1: 93%
Metabolism	trastuzumab emtansine undergoes catabolism by proteolysis in cellular lysosomes; *in vitro* studies suggest DM1 is metabolized mainly by CYP 3A4.	
	active metabolite(s)	cytotoxic catabolites: lysine-MCC-DM1, MCC-DM1, DM1
	inactive metabolite(s)	no information found
Excretion	catabolites are excreted mainly through bile; minimal elimination in urine	
	urine	minimal
	feces	mainly in bile
	terminal half life	3-4.5 days
	clearance	7-13 mL/day/kg

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Breast cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to trastuzumab[2] or Chinese hamster ovary cell proteins[4]

Caution:
- trastuzumab emtansine (KADCYLA®) is ***NOT interchangeable*** with trastuzumab (HERCEPTIN®) or other trastuzumab-drug conjugates and should not be substituted.[2]
- use with caution in patients with pre-existing ***cardiac dysfunction*** or a left ventricular ejection fraction (LVEF) of 50% or less.[2]
- use with caution in patients who experience ***dyspnea*** at rest due to complications of advanced malignancy and co-morbidities; may be at an increased risk of developing pulmonary events, including interstitial lung disease and pneumonitis.[2]

Special populations: Asian patients have a higher incidence and severity of thrombocytopenia.[2]

Carcinogenicity: no information found.

Mutagenicity: Not mutagenic in Ames test. Trastuzumab emtansine is aneugenic and/or clastogenic in rat bone marrow *in vivo* but not in other mammalian *in vivo* chromosome tests.[2]

Fertility: In animal studies, degeneration of seminiferous tubules with hemorrhage in the testes, increased testes and epididymides weight, as well as hemorrhage and necrosis of the corpus luteum in ovaries have been reported.[2]

Pregnancy: Oligohydramnios, pulmonary hypoplasia, skeletal abnormalities and neonatal death have been reported with trastuzumab. Teratogenicity and embryotoxicity is expected with DM1 due to its mechanism of action. For women of child bearing potential, effective contraception is recommended during treatment and for at least 7 months following the last dose.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk. It is not known whether trastuzumab emtansine is excreted in human milk; however, trastuzumab has been detected in breast milk in animal studies. Therefore, it is suggested that women should discontinue nursing prior to treatment with trastuzumab emtansine. Women may begin nursing 6 months after treatment is finished.[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, and/or determined to be clinically important.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (15%, severe 5%)
	bleeding (33%, severe 2%)
	neutropenia (8%, severe 2%); nadir day 8
	thrombocytopenia (31%, severe 15%)
cardiac	***left ventricular dysfunction*** (2%, severe <1%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
eye	blurred vision (5%)
	conjunctivitis (4%)
	dry eye (4%)
	lacrimation increased (3%)
gastrointestinal	*emetogenic potential:* low[7]
	abdominal pain (19%, severe 1%)
	constipation (27%, severe <1%)
	diarrhea (25%, severe 2%)
	dry mouth (17%)
	dyspepsia (9%)
	nausea (40%, severe 1%)
	stomatitis (14%, severe <1%)
	vomiting (19%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* irritant[8]; under review - see paragraph following **Side Effects** table
	asthenia (18%, severe <1%)
	chills (8%)
	fatigue (37%, severe 2%)
	infusion-related reaction (1%); see paragraph following **Side Effects** table
	injection site extravasation[9-11]; see paragraph following **Side Effects** table
	peripheral edema (7%)
	pyrexia (19%, severe <1%)
hepatobiliary	hepatitis[12] (<1%)
	hepatotoxicity[12] (<1%)
	nodular regenerative hyperplasia (NRH)/portal hypertension (<1%); see paragraph following **Side Effects** table
immune system	***drug hypersensitivity*** (2%)
infections and infestations	urinary tract infection (12%, severe 1%)
investigations; see paragraph following **Side Effects** table	***transaminases increase*** (29%, severe 8%)
	alkaline phosphatase increase (5%, severe <1%)
	hyperbilirubinemia (2%)
metabolism and nutrition	***hypokalemia*** (10%, severe 3%)
musculoskeletal and connective tissue	arthralgia (20%, severe 1%)
	musculoskeletal pain (37%, severe 2%)
	myalgia (14%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
nervous system	dizziness (11%, severe <1%)
	dysgeusia (8%)
	headache (29%, severe 1%)
	peripheral neuropathy (22%, severe 2%); see paragraph following **Side Effects** table
psychiatric	insomnia (12%, severe <1%)
respiratory, thoracic and mediastinal	cough (18%, severe <1%)
	dyspnea (12%, severe 1%)
	epistaxis (23%, severe <1%)
	interstitial lung disease/pneumonitis (1%); see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (4%)
	palmar-plantar erythrodysaesthesia (1%)
	pruritus (6%, severe <1%)
	rash (12%)
vascular	hypertension (5%, severe 1%)

Adapted from standard reference[2] unless specified otherwise.

Extravasation may cause erythema, tenderness, skin irritation, pain or swelling at the infusion site. Reactions are usually mild and are observed more frequently within 24 hours of extravasation. A few serious cases of epidermal injury or necrosis have been observed within a few days after infusion, with reports of burning sensation, blistering, ulcerative injury, and skin necrosis.[9-11] No specific treatment/antidote is recommended. For more information on the management of extravasation reactions, see BC Cancer Systemic Therapy Policy III-20 ***Prevention and Management of Extravasation of Chemotherapy***.

Infusion-related reactions ranging from flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported. In most cases, these symptoms were not severe and reactions resolved over several hours to one day after the infusion was terminated. Infusion rate may be slowed or interrupted for infusion-related reactions. Consider permanently discontinuing treatment for severe hypersensitivity reactions, including anaphylaxis or respiratory distress.[2] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Interstitial lung disease (ILD), including pneumonitis, has been reported, with some cases leading to acute respiratory distress syndrome or a fatal outcome. Symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not be part of an infusion-related reaction. Permanently discontinue treatment if patient develops ILD or pneumonitis.[2]

Hepatotoxicity, mainly in the form of asymptomatic increases in serum transaminases, has been observed with trastuzumab emtansine. However, hyperbilirubinemia and nodular regenerative hyperplasia (NRH), with fatalities, have also been reported. Effect on transaminases may be cumulative; however elevated transaminases usually improve to grade 1 or normal within 30 days of final treatment. Elevated transaminases and hyperbilirubinemia may require an interruption of therapy, as well as a dose reduction. Refer to protocol by which patient is being treated. Permanently discontinue treatment if patient develops[2]:

- grade 4 increases in transaminases (greater than twenty times the upper limit of normal) OR bilirubin (greater than ten times the upper limit of normal), or

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- transaminases greater than three times the upper limit of normal AND concomitant bilirubin greater than two times the upper limit of normal, or
- nodular regenerative hyperplasia.

Left ventricular dysfunction with left ventricular ejection fraction (LVEF) less than 40% has been observed with trastuzumab emtansine. ECG or MUGA scanning should be performed prior to and regularly throughout treatment. Long term effect of trastuzumab emtansine on cardiotoxicity is not known. If LVEF is less than 40%, or 40-45% with a decrease of 10% or more from baseline, hold treatment and repeat LVEF assessment within three weeks. After reassessment, discontinue treatment if LVEF is still less than 40% or has not recovered to within 10% of baseline.[2]

Peripheral neuropathy has been reported in 22% of patients receiving trastuzumab emtansine. Hold treatment in patients with grade 3 or 4 peripheral neuropathy until symptoms improve to grade 2 or better and consider dose reduction when restarting.[2]

INTERACTIONS:

The DM1 moiety is a substrate of **CYP 3A4**. Strong CYP 3A4 inhibitors may increase DM1 plasma levels and hence, its toxicity; therefore avoid concurrent use if possible. If concurrent use is unavoidable, consider delaying trastuzumab emtansine treatment until the strong CYP 3A4 inhibitor has been cleared from the system (approximately three half-lives of the inhibitor). Monitor patient for adverse reactions related to trastuzumab emtansine.[2]

SUPPLY AND STORAGE:

Injection**:** Hoffmann-la Roche supplies trastuzumab emtansine as 100 mg or 160 mg vials of preservative-free powder. Refrigerate.[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 dilute with or administer through an intravenous line containing dextrose solutions[2]
- use a 0.2 micron in-line or 0.22 micron polyethersulfone (PES) filter to administer infusions prepared in NS; filter is optional for infusions prepared in 0.45% NS[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[1]	not recommended
Intermittent infusion[5,13,14]	***Initial dose: over 90 minutes*** ***Subsequent doses: over 30 minutes*** • administer using a 0.2 micron (or equivalent) in-line filter if prepared in NS
Continuous infusion	no information found

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

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[5,13,14]

Cycle Length:
3 weeks: ***3.6 mg/kg*** (range 2.4-3.6 mg/kg) ***IV for one dose on day 1***
(total dose per cycle 3.6 mg/kg [range 2.4-3.6 mg/kg])

Do not re-escalate dose after dose reduction.[2]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, consider dose reduction schedule below[2]:

Thrombocytopenia (Platelet count **x** 10^9/L)	**Management**
grade 3 (25-49)	hold until recovery to grade 1 or less (platelets ≥75), then treat at the same dose level.
grade 4 (<25)	hold until recovery to grade 1 or less (platelets ≥75), then reduce one dose level.

Dosage in renal failure[2]*:* mild or moderate impairment: no adjustment recommended
severe impairment: no information found

Dosage in hepatic failure[12]*:* mild or moderate impairment (Child-Pugh A,B): no adjustment required for starting doses
severe impairment (Child-Pugh C): no information found

Dosage in dialysis: no information found

Children: no information found

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