

**DRUG NAME: Trastuzumab emtansine****SYNONYM(S):** T-DM1, trastuzumab-DM1, trastuzumab-MCC-DM1, ado-trastuzumab emtansine<sup>1</sup>**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.<sup>2</sup>

**PHARMACOKINETICS:**

|              |  |   |
|--------------|--|---|
| Distribution | systemic accumulation is not observed with repeat doses <sup>1</sup>   |   |
|              | cross blood brain barrier?   | no information found                                |
|              | volume of distribution <sup>3</sup>  | 3.13 L  |
|              | plasma protein binding <sup>1</sup>  | DM1: 93%  |
| Metabolism   | trastuzumab emtansine undergoes catabolism by proteolysis in cellular lysosomes; <i>in vitro</i> 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<sup>2</sup> unless specified otherwise.**USES:****Primary uses:**

\*Breast cancer

\*Health Canada approved indication

**Other uses:****SPECIAL PRECAUTIONS:****Contraindications:**

- history of hypersensitivity reaction to trastuzumab<sup>2</sup> or Chinese hamster ovary cell proteins<sup>4</sup>

**Caution:**

- Trastuzumab emtansine (KADCYLA®) is **NOT interchangeable** with trastuzumab (HERCEPTIN®) and should not be substituted.<sup>2</sup>
- Use with caution in patients with pre-existing cardiac dysfunction or a left ventricular ejection fraction (LVEF) of 50% or less.<sup>2</sup>
- 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.<sup>2</sup>

**Special populations:** *Asian patients* have a higher incidence and severity of thrombocytopenia.<sup>2</sup>

**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.<sup>2</sup>

**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.<sup>2</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>1</sup> There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Oligohydramnios, pulmonary hypoplasia, skeletal abnormalities and neonatal death has been reported with trastuzumab. Teratogenicity and embryotoxicity is expected with DM1 due to its mechanism of action.<sup>2</sup>

**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.<sup>2</sup>

**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.<sup>5</sup>

| ORGAN SITE  | SIDE EFFECT   |
|---|---|
| Clinically important side effects are in <b>bold, italics</b> |   |
| blood and lymphatic system/ febrile neutropenia               | anemia (15%, severe 5%)   |
|   | bleeding (33%, severe 2%)   |
|   | neutropenia (8%, severe 2%); nadir day 8  |
|   | <b>thrombocytopenia</b> (31%, severe 15%)   |
| cardiac   | <b>left ventricular dysfunction</b> (2%, severe <1%); see paragraph following <b>Side Effects</b> table |
| eye   | blurred vision (5%)   |
|   | conjunctivitis (4%)   |
|   | dry eye (4%)  |
|   | lacrimation increased (3%)  |

| ORGAN SITE  | SIDE EFFECT   |
|---|---|
| Clinically important side effects are in <b>bold, italics</b>     |   |
| gastrointestinal  | <i>emetogenic potential: low</i> <sup>6</sup>   |
|   | 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              | <i>extravasation hazard: irritant</i> <sup>7</sup>  |
|   | asthenia (18%, severe <1%)  |
|   | chills (8%)   |
|   | <b>fatigue</b> (37%, severe 2%)   |
|   | <b>infusion-related reaction</b> (1%); see paragraph following <b>Side Effects</b> table  |
|   | injection site reactions (erythema, tenderness, skin irritation, pain, or swelling at injection site after extravasation); usually mild, observed more frequently within 24 h of infusion |
|   | peripheral edema (7%)   |
|   | pyrexia (19%, severe <1%)   |
| hepatobiliary   | hepatitis <sup>8</sup> (<1%)  |
|   | hepatotoxicity <sup>8</sup> (<1%)   |
|   | <b>nodular regenerative hyperplasia (NRH)/portal hypertension</b> (<1%); see paragraph following <b>Side Effects</b> table  |
| immune system   | <b>drug hypersensitivity</b> (2%)   |
| infections and infestations                                       | urinary tract infection (12%, severe 1%)  |
| investigations; see paragraph following <b>Side Effects</b> table | <b>transaminases increase</b> (29%, severe 8%)  |
|   | alkaline phosphatase increase (5%, severe <1%)  |
|   | <b>hyperbilirubinemia</b> (2%)  |
| metabolism and nutrition  | <b>hypokalemia</b> (10%, severe 3%)   |
| musculoskeletal and connective tissue                             | arthralgia (20%, severe 1%)   |
|   | <b>musculoskeletal pain</b> (37%, severe 2%)  |
|   | myalgia (14%, severe 1%)  |
| nervous system  | dizziness (11%, severe <1%)   |
|   | dysgeusia (8%)  |
|   | headache (29%, severe 1%)   |
|   | <b>peripheral neuropathy</b> (22%, severe 2%); see paragraph following <b>Side Effects</b> table  |
| psychiatric   | insomnia (12%, severe <1%)  |

| ORGAN SITE   | SIDE EFFECT   |
|--|---|
| Clinically important side effects are in <b><i>bold, italics</i></b> |   |
| respiratory, thoracic and mediastinal                                | cough (18%, severe <1%)   |
|  | dyspnea (12%, severe 1%)  |
|  | epistaxis (23%, severe <1%)   |
|  | <b><i>interstitial lung disease/pneumonitis</i></b> (1%); see paragraph following <b>Side Effects</b> table |
| skin and subcutaneous tissue   | alopecia (4%)   |
|  | palmar-plantar erythrodysesthesia (1%)  |
|  | pruritus (6%, severe <1%)   |
|  | rash (12%)  |
| vascular   | hypertension (5%, severe 1%)  |

Adapted from standard reference<sup>2</sup> unless specified otherwise.

**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.<sup>2</sup>

**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.<sup>2</sup> For management of hypersensitivity reactions, see [BC Cancer Protocol Summary for Management of Hypersensitivity Reactions to Chemotherapeutic Agents](#).

**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<sup>2</sup>:

- 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
- 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.

**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; see **Dosage Guidelines**.<sup>2</sup>

**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.<sup>2</sup>

**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.<sup>2</sup>

**SUPPLY AND STORAGE:**

**Injection:** Hoffmann-la Roche supplies trastuzumab emtansine as 100 mg or 160 mg vials of preservative-free powder. Refrigerate.<sup>2</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 dilute with or administer through an intravenous line containing dextrose solutions.<sup>2</sup>
- Use a 0.2 micron in-line or 0.22 micron polyethersulfane (PES) filter to administer infusions prepared in 0.9% NS. A filter is optional for infusions prepared in 0.45% NS.<sup>2</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 <sup>1</sup>                   | not recommended  |
| <b><i>Intermittent infusion<sup>2,9</sup></i></b> | <b><i>Initial dose: over 90 minutes</i></b> (observe at least 90 minutes post-infusion)<br><b><i>Subsequent doses: over 30 minutes</i></b> (observe at least 30 minutes post-infusion) |
| 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*<sup>2,9</sup>:

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.<sup>2</sup>

| Dose Reduction Schedule | Dose Level (mg/kg) |
|-------------------------|--------------------|
| Starting dose           | 3.6                |
| First dose reduction    | 3                  |
| Second dose reduction   | 2.4                |

*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<sup>2</sup>:

**Thrombocytopenia:** Platelet ( $\times 10^9/L$ )

|                 |  |
|-----------------|--|
| Grade 3 (25-49) | Hold until recovery to $\leq$ grade 1 (platelets $\geq 75$ ), then treat at the same dose level. |
| Grade 4 (<25)   | Hold until recovery to $\leq$ grade 1 (platelets $\geq 75$ ), then reduce one dose level.        |

*Dosage in renal failure*<sup>2</sup>: mild or moderate impairment: no adjustment recommended  
severe impairment: no information found

*Dosage in hepatic failure*<sup>8</sup>: **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

**REFERENCES:**

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7. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 June 2012.
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