DRUG NAME: Trastuzumab

SYNONYM(S): anti-c-erB-2; anti-ERB-2; MOAB HER2; rhuMAb HER2[1]

COMMON TRADE NAME(S): HERCEPTIN®; HERZUMA® (biosimilar), TRAZIMERA® (biosimilar), OGIVRI® (biosimilar)

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Trastuzumab is a human monoclonal IgG antibody which selectively targets HER2, a human epidermal growth factor receptor (EGFR). Trastuzumab inhibits the growth of tumour cells that overexpress HER2 on the surface of breast, gastric, ovarian, lung, and prostate cancer cells.[2,3] Mechanisms involved include: decreasing VEGF production, activating antibody-dependent cell-mediated cytotoxicity, G0/G1 cell cycle cytotoxicity, and inhibiting intracellular signaling pathways.[2,4,5]

PHARMACOKINETICS:

Interpatient variability	interpatient variability noted in clearance and volume of distribution[2,6]	
Distribution	steady state, AUC, C_{max}, C_{min} are lower in metastatic gastric cancer than metastatic breast cancer [2]; steady state trough levels are similar between weekly and 3-weekly regimens[2,7,8]	
	cross blood brain barrier?	unlikely, due to large molecule size[1,9,10]
	volume of distribution	3-4L
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	via the reticuloendothelial system[11]	
	urine	no information found
	feces	no information found
	terminal half life	12-29 days; shorter half life in metastatic gastric cancer due to increased clearance
	clearance	0.225-0.378 L/day; increased with more metastatic sites[2,6]
Elderly	no differences reported	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Breast cancer

*Gastric cancer

Other uses:

*Health Canada approved indication

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Developed: 1 January 2013
Revised: 1 December 2021

SPECIAL PRECAUTIONS:

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

Caution:
- in patients with pre-existing cardiac dysfunction or a left ventricular ejection fraction (LVEF) of 55% or less[2,12]
- in patients with pre-existing pulmonary disease or extensive pulmonary tumour involvement[1]; patients who experience dyspnea at rest due to comorbidities or advanced malignancy may be at increased risk of a fatal infusion reaction.[2]

Special populations:
- patients aged 65 years and older may be at greater risk for cardiac dysfunction and hematologic toxicities (leukopenia and thrombocytopenia)[2]
- patients who received prior adjuvant therapy with anthracyclines for treatment of early breast cancer are at greater risk of developing cardiotoxicity[1]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Trastuzumab is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: Formal fertility studies have not been conducted in women. No evidence of impaired fertility was reported in animal studies.[2]

Pregnancy: FDA Pregnancy Category D. There is 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).
Impaired fetal renal growth and function, intrauterine growth retardation, and skeletal abnormalities associated with oligohydramnios during the second and third trimesters have been reported.[2] Women of childbearing potential are advised to use effective contraception during treatment and for at least 7 months post treatment.[13]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, trastuzumab was detected in the milk of lactating monkeys, although no adverse effects on growth or development were seen.[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.[14-16]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (4%)[1]
	leukopenia (3%)[1]
cardiac	arrhythmia (3%)[1]
	congestive heart failure (2%; severe <1%)[2,17]; see paragraph following **Side Effect** table
	palpitations (3%)

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Developed: 1 January 2013
Revised: 1 December 2021

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	tachycardia (1%)
gastrointestinal	*emetogenic potential: low*[18]
	abdominal pain (2%)
	constipation (2%)
	diarrhea (7%)
	dyspepsia (2%)
	gastritis (1%)
	nausea (6-14%)[2,19]
	stomatitis (2%)
	vomiting (4-28%)
general disorders and administration site conditions	*extravasation hazard: none*[20]
	asthenia (5%)
	chills (5%)
	fatigue (8%)
	fever (6%)
	influenza-like illness (2%)
	infusion-related reaction (21-40%, severe 1%)[1]; see paragraph following **Side Effects** table
	non-cardiac chest pain (3%)
	peripheral edema (5%)
immune system	allergic reaction (3%)
infections and infestations	herpes zoster (1%)
	influenza (4%)
	nasopharyngitis (8%)
	pharyngitis (1%)
	rhinitis (2%)
	sinusitis (2%)
	upper respiratory tract infection (3%)
	urinary tract infection (2-5%)[1,2]
investigations	alkaline phosphatase, elevated[21]
	ALT, elevated[21]
	AST, elevated[21]
	bilirubin, elevated (1%)
	ejection fraction, decreased (4-10%)[2,17]; see paragraph following **Side Effect** table
	weight gain (2%)
	arthralgia (8%)

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Developed: 1 January 2013
Revised: 1 December 2021

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
musculoskeletal and connective tissue	back pain (5%)
	bone pain (3%)
	chest wall pain (2%)
	muscle spasms (3%)
	myalgia (4%)
	pain in extremity (4%)
	shoulder pain (2%)
nervous system	dizziness (4%)
	headache (10%)
	paresthesia (2%)
	vertigo (2%)
psychiatric	anxiety (2%)
	depression (3%)
	insomnia (4%)
renal and urinary	cystitis (1%)
reproductive system and breast disorders	breast pain (1%)
respiratory, thoracic and mediastinal	cough (5%)
	dyspnea (3%)
	epistaxis (1%)
	pharyngolaryngeal pain (2%)
	rhinitis (2%)
skin and subcutaneous tissue	erythema (1%)
	nail disorder (3%)
	pruritus (2%)
	rash (4%)
vascular	hot flashes (6%)
	hypertension (4%)
	lymphedema (3%)

Adapted from standard reference[2] unless specified otherwise.

Cardiotoxicity has been reported with trastuzumab. Signs and symptoms include: dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, congestive heart failure (CHF), or a reduced ejection fraction of 10% or greater.[2,11] Cardiac dysfunction from trastuzumab is not dose-related and is reported to be highly reversible so patients have relatively good prognosis following CHF or LVEF dysfunction.[12,17,22,23] LVEF usually returns toward baseline during the 1.5 months post-trastuzumab treatment[2,11,22]; however, some cases have resulted in disabling heart failure, thrombosis and stroke, and/or death.[2,11]

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Developed: 1 January 2013
Revised: 1 December 2021

Risk factors for trastuzumab-related cardiotoxicity include:[11,12,24-27]
- older age (>65 years)
- prior or concurrent use of antihypertensive medications
- higher cumulative dose of anthracycline prior to trastuzumab
- a lower left ventricular ejection fraction (LVEF) at baseline
- a declining LVEF (<55%)
- a low LVEF prior to or following paclitaxel treatment
- a higher body mass index (>25) at screening

An increase in cardiac events is observed when trastuzumab is administered after anthracycline-containing chemotherapy compared to non-anthracycline-containing chemotherapy. The incidence is more marked when trastuzumab is administered concurrently, rather than sequentially, with a taxane.[27] There is some uncertainty whether smoking, diabetes, hypothyroidism, or hyperlipidemia is associated with trastuzumab-related cardiotoxicity.[12,24] Prior or concurrent radiation does not increase cardiac events, but may increase the incidence of leukopenia.[2,28,29] There is inadequate long term data, however, to correlate cardiac dysfunction from trastuzumab with concurrent or prior radiation.[2,28] Trastuzumab interrupts the HER2 signalling pathway in the heart which maintains normal growth, repair, and survival of cardiac cells. This results in changes to cardiac contractility, but does not cause myocardial cell death.[12,17,22] Suggested management for trastuzumab-related cardiotoxicity includes withholding trastuzumab for approximately 3 weeks if LVEF falls 10-15 ejection points below baseline and/or below 50%.[2,12] Trastuzumab can be resumed once LVEF improves. If the LVEF does not improve within approximately 3 weeks, consider discontinuing trastuzumab.[2] Trastuzumab may be considered in patients with a LVEF less than 50% if their risk of disease recurrence is very high.[12] The LVEF should be assessed prior to starting trastuzumab, repeated every 3 months during treatment, and then, every 6 months following completion of treatment until 24 months from the last dose of trastuzumab. For early breast cancer patients who received anthracycline-based chemotherapy, yearly monitoring of LVEF up to 5 years or longer from the last dose of trastuzumab is suggested.[27] Refer to protocol by which patient is being treated.

Infusion-related reactions range from mild reactions of chills and/or fever (occurring in 40% of patients with first infusion) to mild-moderate reactions of nausea, vomiting, pain, rigors, headache, cough, dizziness, dyspnea, rash, and asthenia. Severe reactions include hypotension, hypertension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. Pre-existing pulmonary disease or co-morbidities may increase risk of pulmonary toxicities or a fatal reaction. Clinical course is variable; initial improvement may be followed by clinical deterioration and death. Management of infusion-related reactions includes decreasing the rate for mild or moderate reactions and interrupting the infusion in patients experiencing dyspnea or hypotension. Consider discontinuing treatment for severe reactions such as anaphylaxis, angioedema, pneumonitis, or respiratory distress. Patients who react to the initial trastuzumab infusion may receive further treatment after complete resolution of symptoms. Infusion duration may be increased at the physician's discretion. Symptoms are managed with diphenhydramine, acetaminophen, meperidine, epinephrine, corticosteroids, oxygen, bronchodilators, or IV fluids. Patients experiencing infusion-related symptoms should not drive or use machines until symptoms resolve completely.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anthracycline chemotherapy[2,10,11,27,30]	increase in trastuzumab-induced cardiac dysfunction	negative inotropic effect on the heart	avoid use of anthracyclines concurrently with trastuzumab
paclitaxel[2,10,11,30]	1.5 fold increase in trastuzumab serum levels	mechanism unclear; animal studies report a 2 fold decrease in trastuzumab clearance	monitor for signs of cardiac dysfunction

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Developed: 1 January 2013
Revised: 1 December 2021

SUPPLY AND STORAGE:

Biosimilar formulations of trastuzumab are available.

***Injection*:**
Hoffmann-La Roche Limited supplies trastuzumab (HERCEPTIN®) as 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution. Refrigerate.[2]

Celltrion Healthcare Co. Ltd. (distributed by Teva Canada Limited) supplies trastuzumab (HERZUMA®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.[31]

BGP Pharma ULC supplies trastuzumab (OGIVRI®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.[32]

Pfizer Canada ULC supplies trastuzumab (TRAZIMERA®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.[33]

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:

- Benzyl alcohol should not be administered intrathecally due to the risk of anaphylaxis and increased potential for neurotoxicity.[34,35] For intrathecal administration of trastuzumab or in patients with a known hypersensitivity to benzyl alcohol:
  - reconstitute vial with sterile water for injection instead of the supplied preservative-containing diluent[2,35,36]
  - use immediately; discard unused portion[2,37]
- Trastuzumab should not be further diluted or administered with dextrose (5%) solution as it may cause aggregation of the protein.[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	has been given[38]
Intramuscular	no information found
Direct intravenous	do not use[2]

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Developed: 1 January 2013
Revised: 1 December 2021

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

Intermittent infusion	***over 30-90 minutes***[2,25,39-58] ***3-weekly dosing:*** • ***loading dose over 90 minutes;*** • ***1st maintenance dose over 60 minutes;*** • ***2nd and further maintenance doses over 30 minutes if no adverse reactions*** ***Weekly dosing:*** • ***loading dose over 60 minutes;*** • ***maintenance doses over 30 minutes if no adverse reactions***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	has been used[34-37,59-61]
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: ***weekly***[45,62-66]:	***Loading dose: 4 mg/kg IV*** for one dose on day 1 of ***first cycle*** ***Maintenance dose: 2 mg/kg IV*** for one dose on day 1 of ***each subsequent cycle***
	3 weeks[42-44,46-58,67-69]:	***Loading dose: 8 mg/kg IV*** for one dose on day 1 of ***first cycle*** ***Maintenance dose: 6 mg/kg IV*** for one dose on day 1 of ***each subsequent cycle***
	4 weeks[70-72]	***Loading dose: 8 mg/kg IV*** for one dose on day 1 of ***first cycle*** ***Maintenance dose: 6 mg/kg IV*** for one dose on day 1 of ***each subsequent cycle***

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Developed: 1 January 2013
Revised: 1 December 2021

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

	Cycle Length:	
	3 weeks[73]:	Loading dose: 6 mg/kg IV for one dose on days 1, 8, and 15 of first cycle
		Maintenance dose: 6 mg/kg IV for one dose on day 1 only of each subsequent cycle
	4 weeks[74,75]:	440 mg IV for one dose on day 1
	Using a reloading dose has been recommended to quickly regain a therapeutic serum level after a treatment delay; however the optimal way to reload trastuzumab after interruption of maintenance therapy is unclear. Trastuzumab has a long elimination half-life so serum level declines slowly with short treatment delays. In addition, the minimal therapeutic serum level is not clearly defined, since the targeted serum level in dosing design[7,76,77] is based on in vitro tumour growth inhibition[78] and is lower than the actual steady state level observed in efficacy trials.[79] See protocol by which patient is being treated.	
Concurrent radiation:	***3 weeks***[28,29,42-44,46-48]	***Loading dose: 8 mg/kg IV*** for one dose on day 1 of ***first cycle***
		Maintenance dose: 6 mg/kg IV for one dose on day 1 of ***subsequent cycles***
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required[2]	
Dosage in hepatic failure:	no information found	
Dosage in dialysis:	no significant removal[80]	

Children:

Intravenous:	safety and effectiveness not established[2]

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Revised: 1 December 2021

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