DRUG NAME: Pertuzumab

SYNONYM(S):

COMMON TRADE NAME(S): PERJETA®

CLASSIFICATION: monoclonal antibody

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

MECHANISM OF ACTION:

Pertuzumab is a recombinant humanized monoclonal antibody that blocks the extracellular dimerization of the human epidermal growth factor receptor 2 protein (HER2) with other HER family members. This inhibits ligand-initiated intracellular signalling, resulting in cell growth arrest and apoptosis. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity.[1] Pertuzumab binds to a different antigenic region of the HER2 extracellular domain than trastuzumab.[2]

PHARMACOKINETICS:

Distribution	variable; possibly by tumour type	
	cross blood brain barrier?	no information found
	volume of distribution	3.53-7.05 L
	plasma protein binding	no information found
Metabolism	cleared principally by catabolism	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	mean half life is variable	
	urine	no information found
	feces	no information found
	terminal half life	11-22 days
	clearance	0.232-0.329 L/day

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Breast cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***decreased left ventricular ejection fraction*** (LVEF) has been reported with pertuzumab; patients treated with prior anthracyclines or radiotherapy to the chest may be at higher risk[1]
- ***infusion and hypersensitivity reactions*** have been reported[1]

Special populations: Asian patients may be at higher risk of **febrile neutropenia** than general population (26% vs. 14%) when pertuzumab is used with chemotherapy.[1]

Carcinogenicity: no information found.

Mutagenicity: no information found.

Fertility: no formal studies conducted; no adverse effects on reproductive organs were reported in male or female monkeys in repeat-dose toxicity studies.[1]

Pregnancy: FDA Pregnancy Category D.[3] 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). Embryo-fetal toxicities (e.g., oligohydramnios, delayed fetal kidney development, and embryo-fetal death) have been reported in animal studies and are likely during all trimesters of pregnancy. Effective contraception should be used during and for six months after pertuzumab treatment in women with childbearing potential and men with female partners of childbearing potential.[1]

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, and/or determined to be clinically important. **Incidence data in the Side Effect table is based on pertuzumab monotherapy data where possible; in some cases, incidence data based on combination therapy with trastuzumab has been included and is indicated with an asterisk (*).**

ORGAN SITE	SIDE EFFECT
blood and lymphatic system/ febrile neutropenia	anemia (>10%)[1,4]
	neutropenia* (1%, severe 1%)[5]
cardiac	CHF* (1%, severe 1%)[5]
	left ventricular dysfunction* (7-14%, severe 1%)[1,4,5]; see paragraph following **Side Effects** table
eye	lacrimation, increased (>10%)[1]
gastrointestinal	*emetogenic potential: low*[6]
	abdominal pain/ distension (7-12%, severe 3%)
	diarrhea (48-51%, severe 3-7%)
	dysgeusia/ ageusia (>10%)[1]
	mucositis/ stomatitis* (3-10%)[4,5]
	nausea (24-35%)
	oropharyngeal pain (7%, severe 3%)
	vomiting (15-24%, severe 2%)
general disorders and administration site conditions	*extravasation hazard: none*[7]
	edema (>10%)[1]
	fatigue/ asthenia (17-22%, severe 2-3%)

ORGAN SITE	SIDE EFFECT
	fever (>10%)[1]
	flu-like syndrome (>10%)[1]
	infusion reactions (13-19%)[1]; see paragraph following **Side Effects** table
immune system	***hypersensitivity reactions*** (11%, severe 2-5%)[1]; see paragraph following **Side Effects** table
investigations	weight decrease (8%)[1]
metabolism and nutrition	anorexia (5-10%)
musculoskeletal and connective tissue	arthralgia/ myalgia (10%)
	back/ neck pain (10-17%)[1,8]
	extremity pain (3%)
	muscle spasms/ weakness* (12%)[1,9]
nervous system	dizziness (>10%)[1]
	headache (7-12%)
	paresthesias* (11%)[1,9]
psychiatric	insomnia (>10%)[1]
respiratory, thoracic and mediastinal	cough* (14%)[9]
	dyspnea (10%)
skin and subcutaneous tissue	alopecia* (1%)[5]
	paronychia (1-10%)[1]
	pruritus (10%)
	rash (10-20%, severe 2%)

Adapted from standard reference[4,8] unless specified otherwise.

Infusion reactions may include fever, chills, fatigue, headaches, asthenia, hypersensitivity, and vomiting. The majority of reactions are mild or moderate in severity and resolve upon treatment. Infusion rate may be slowed or interrupted after a reaction; discontinue infusion immediately for severe hypersensitivity reaction.[1] For management of hypersensitivity reactions, see BCCA Protocol Summary for Management of Hypersensitivity Reactions to Chemotherapeutic Agents BCCA Protocol SCDRUGRX.

Cardiac toxicity: Decreased left ventricular ejection fraction (LVEF) has been reported with drugs that block HER2 activity. However, pertuzumab does not seem to further increase the incidence of symptomatic congestive heart failure or decreased LVEF when used in combination with trastuzumab and docetaxel. Cardiac assessments should be performed at baseline and repeated at regular intervals. Pertuzumab should be withheld if LVEF falls to less than 40% or is between 40-45% and associated with a 10% decrease from pre-treatment value. If LVEF does not improve or declines further, consider permanent discontinuation of pertuzumab.[1] Refer to protocol by which patient is being treated.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
capecitabine[1]	no influence on pertuzumab pharmacokinetics		

AGENT	EFFECT	MECHANISM	MANAGEMENT
docetaxel[1]	no influence on pertuzumab pharmacokinetics		
erlotinib[1]	no influence on pertuzumab pharmacokinetics		
gemcitabine[1]	no influence on pertuzumab pharmacokinetics		
trastuzumab[1]	no influence on pertuzumab pharmacokinetics		

SUPPLY AND STORAGE:

Injection: Hoffman-La Roche supplies pertuzumab as 420 mg single-use (preservative free) vials of liquid concentrate in a concentration of 30 mg/mL. Refrigerate. Protect from light. Do NOT freeze. Do NOT shake. Inactive ingredient: sucrose.[1]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: Pertuzumab is chemically and physically unstable in dextrose (5%) solution.[1]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[1]
Intermittent infusion[1,10]	***Loading dose: over 60 min*** ***Maintenance doses: over 30-60 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*:**

BCCA usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: 3 weeks[1,10]:	***Loading dose: 840 mg IV for one dose on day 1 of first cycle***; ***Maintenance dose: 420 mg IV for one dose on day 1 of each subsequent cycle.*** Dose reductions are not recommended. For treatment interruption greater than 6 weeks: repeat loading dose of 840 mg, then resume maintenance dose of 420 mg every three weeks thereafter.[1]
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required for creatinine clearance ≥30 mL/min[1]; no information found for creatinine clearance <30 mL/min[1]	
	Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu mol/L}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	no information found	
Dosage in dialysis:	no information found	

Children: safety and efficacy have not been established[1]

REFERENCES:

1. Hoffmann-La Roche Limited. PERJETA® product monograph. Mississauga, Ontario; 12 April 2013.
2. Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. Drugs 2012;72(3):353-360.
3. Genentech Inc. PERJETA® full prescribing information. South San Francisco, CA, USA; June 2012.
4. Gianni L, Llado A, Bianchi G, et al. Open-label, phase II , multicenter, randomized study of the efficacy and safety of two dose levels of pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28(7):1131-1137.
5. Gianni L, Pienkowski T, Im Y, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomized multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
6. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
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.
8. Cortes J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30(14):1594-1600.

9. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28(7):1138-1144.
10. BC Cancer Agency Breast Tumour Group. (UBRAVPTRAD) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer Using Pertuzumab, Trastuzumab (HERCEPTIN®), and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer. Vancouver, British Columbia: BC Cancer Agency; 1 November 2013.