Drug Monograph

A - Drug Name

PERTuzumab

COMMON TRADE NAME(S): Perjeta®

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B - Mechanism of Action and Pharmacokinetics

Pertuzumab is a recombinant humanized monoclonal antibody that inhibits the dimerization of HER2 with other HER family receptors, most notably HER3. It binds to a different epitope of the HER2 extracellular domain than trastuzumab. Downstream inhibition of MAP kinase and PI3K cell signaling pathways result in cell growth arrest or apoptosis. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity, similar to trastuzumab.

Absorption	Steady state concentration of pertuzumab is reached after the first maintenance dose when the standard pertuzumab regimen is administered (pertuzumab 840 mg IV loading dose followed by 420 mg IV every three weeks).	
Metabolism	Not been directly studied. Antibodies are generally cleared by catabolism.	
Elimination	Half-life	11.4-12.2 days in metastatic breast cancer; up to 22.3 days in advanced solid tumour patients

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C - Indications and Status

Health Canada Approvals:

- In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
- In combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer with lymph node positive and/or hormone receptor negative disease.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse effects were observed in ≥ 1% of early breast cancer patients in the phase III pertuzumab clinical trial arm with trastuzumab and chemotherapy. Only adverse effects with a higher incidence than the placebo + trastuzumab and chemotherapy arm are listed. Severe adverse events from other studies or post-marketing, may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (2%)	E D
	Hypertension (11%)	E
Dermatological	Dry skin (13%)	E
	Other - Radiation-skin reaction (13%)	E D
	Palmar-plantar erythrodysesthesia syndrome (PPES) (9%)	E
	Rash, pruritus (26%)	E
Gastrointestinal	Abdominal pain (12%)	E
	Anorexia, weight loss (24%)	E
	Dehydration (4%)	E
	Diarrhea (71%) (10% severe)	E
	Mucositis (28%)	E
	Nausea, vomiting (69%) (2% severe)	I E
General	Fatigue (49%) (4% severe)	E

Hematological	Myelosuppression ± infection, bleeding (28%) (including febrile neutropenia – 12%)	E
Hypersensitivity	Hypersensitivity (3%) (may be severe)	I
	Infusion related reaction (21%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (7%) (↓ K, ↓ Mg, ↓PO4)	E
	Tumor lysis syndrome (rare)	I
Nervous System	Dysgeusia (26%)	E
	Paresthesia (18%)	E
Respiratory	Cough, dyspnea (16%)	E
	Interstitial lung disease (rare)	E
	Other - nasopharyngitis (13%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for pertuzumab include diarrhea, nausea, vomiting, fatigue, mucositis, myelosuppression ± infection, bleeding, dysgeusia, rash, pruritus, anorexia, weight loss, infusion related reaction and paresthesia.

Left Ventricular Ejection Fraction (LVEF) decreases and congestive heart failure have been reported with pertuzumab and other drugs that block HER2 activity. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk. In metastatic breast cancer, the addition of pertuzumab did not appear to increase the incidence of left ventricular systolic dysfunction (LVSD) or LVEF decrease as compared to placebo with docetaxel and trastuzumab. However, in a clinical trial with neoadjuvant treated patients, the incidence of reversible LVSD was higher in the pertuzumab/trastuzumab/docetaxel group than the trastuzumab/docetaxel group. In the early breast cancer adjuvant setting, the incidence of symptomatic heart failure was slightly higher in patients treated with pertuzumab (most of these events were reported in anthracycline-treated patients). Approximately half of the pertuzumab-treated patients who experienced symptomatic heart failure recovered.

There appeared to be an increased risk of **febrile neutropenia** in patients (especially Asian patients) treated with the pertuzumab combination as compared to placebo with docetaxel and trastuzumab, although nadir neutrophil counts were similar between both groups. Febrile neutropenia is most common in cycles 1-3. Mucositis and diarrhea should be treated promptly as these may relate to higher observed rates of febrile neutropenia.

Hypersensitivity reactions, including anaphylaxis, angioedema, and fatal events have been reported. Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment.

Infusion-related reactions (either during or on the day of infusion), including fatal events, have been associated with pertuzumab. In the early breast cancer clinical trial, the incidence of severe events was approximately 1%. Symptoms included fever, chills, fatigue, headache, hypersensitivity, myalgia, dysgeusia and vomiting. Anaphylaxis has been reported.

Adverse effects were reported less frequently after docetaxel discontinuation in metastatic breast cancer. Most adverse effects in the pertuzumab and trastuzumab arm occurred in < 10% except diarrhea, upper respiratory tract infection, rash, headache, fatigue, and arthralgia.

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E - Dosing

Refer to protocol by which patient is being treated.

Patients receiving treatment must have HER2 positive status (score of 3+ by IHC or a ratio of ≥ 2 by ISH) using a validated test.

Pre-medications (prophylaxis for infusion reaction):

- No specific premedications were recommended by the manufacturer.
- For patients who experienced prior infusion reactions, consider premedication with corticosteroids, antihistamines, and/or antipyretics before subsequent pertuzumab infusions.

Adults:

Pertuzumab Loading Dose:

Intravenous: 840 mg over 60 minutes on Day 1*

Then, start **3 weeks later** with:

Pertuzumab Maintenance Dose (q3w):

Intravenous: 420 mg over 30 to 60 minutes on day 1

*In the pivotal phase III trial in metastatic breast cancer, the loading dose was given on day 1 of cycle 1; trastuzumab and docetaxel were given on day 2. If all 3 medications were tolerated in cycle 1, these were administered on day 1 in subsequent cycles. In adjuvant breast cancer, pertuzumab and trastuzumab were started on Day 1 of the first taxane-containing cycle.

Dosage with Toxicity:

Dose reductions are not recommended. Doses are held or discontinued due to toxicity.

If trastuzumab is withheld, pertuzumab should also be withheld. Discontinue pertuzumab if trastuzumab is discontinued.

Cardiotoxicity

Dose Recommendations for Left Ventricular Dysfunction:

Indication	Pre-Treatment LVEF	Cardiotoxicity During Treatment	Action	LVEF at Re-Assessment	Action
Metastatic Breast Cancer	≥ 50%	• Asymptomatic AND • LVEF <40% OR 40%–45% with a fall of ≥10% points below pre-treatment value	Hold trastuzumab and pertuzumab x 3 weeks	• >45% OR • 40%–45% with a fall of <10% points below baseline	Restart trastuzumab and pertuzumab
				• <40% OR • LVEF 40-45% with a fall of ≥10% points below baseline	Discontinue trastuzumab and pertuzumab
Early Breast Cancer	≥ 55%*	• Asymptomatic AND • LVEF <50% with a fall of ≥10% points below baseline*		• ≥50% OR • LVEF <10% points below baseline	Restart trastuzumab and pertuzumab
				• <50% AND	Discontinue

				• LVEF ≥10% points below baseline	trastuzumab and pertuzumab
Any		Symptomatic	Consider discontinuing trastuzumab and pertuzumab.	Not applicable	

*For patients receiving anthracycline-based chemotherapy, a LVEF of ≥50% is required after completion of anthracyclines, before starting Trastuzumab and Pertuzumab.

Management of Infusion-related reactions

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• No specific recommendations can be made at this time.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Other Toxicities

Toxicity	Recommendation
Reversible chemotherapy-induced myelosuppression	Continue pertuzumab, monitor for complications of neutropenia (i.e. infections) and treat appropriately.
Severe diarrhea	Start anti-diarrheal treatment. Hold pertuzumab if no improvement; restart pertuzumab when diarrhea is under control.

Dosage with Hepatic Impairment:

Has not been studied in hepatic impairment.

Dosage with Renal Impairment:

No adjustment required for mild to moderate renal function. Has not been studied in patients with severe renal impairment (< 30 mL/min).

Dosage in the elderly:

No dose adjustment required. No overall differences in safety and efficacy of pertuzumab were observed between adults ≥65 and under 65 years of age, except for diarrhea, which had a higher incidence in patients ≥65 years.

Dosage based on ethnicity:

An increased incidence of neutropenia and febrile neutropenia was observed in Asian patients in both treatment arms of the pivotal phase III trial in metastatic breast cancer as compared with patients of other races. In adjuvant breast cancer, the incidence of febrile neutropenia in Asian patients was higher in the pertuzumab group than the placebo group. The reason for this difference is unknown.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Do not administer as an intravenous push or bolus.
- For pertuzumab, trastuzumab, and taxane combination regimens, pertuzumab and trastuzumab may be administered in any order; however, the taxane should be given after pertuzumab and trastuzumab.
- Pertuzumab and trastuzumab should not be given concurrently with anthracycline therapy. It should start on Day 1 of the first taxane-containing cycle.
- Give loading dose IV over 60 minutes; maintenance dose should be given IV over 30-60 minutes.
- Dilute required dose in 250 mL Normal Saline.
- Do not use D5W for dilution since pertuzumab is chemically and physically unstable in this solution. Do not admix with other drugs.
- Compatible with PVC, polyethylene or non-PVC polyolefin bags.
- Avoid shaking the solution in order to avoid foaming.
- Monitor for infusion reactions for 60 minutes following the initial pertuzumab infusion and for 30 minutes following subsequent infusions.
- Complete the observation period before administering subsequent trastuzumab or chemotherapy.
- Refrigerate unopened vials at 2-8°C; protect from light.

Missed Doses:

- Re-load pertuzumab if time between 2 sequential infusions is 6 weeks or more. The maintenance dose should follow 3 weeks from the re-loading dose.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions:

- Exercise extreme caution with the following patient groups as they have not been studied in clinical trials: Pre-treatment LVEF value of ≤ 50%; a prior history of CHF; decreases in LVEF to <50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360mg/m^2 of doxorubicin or its equivalent.

- Life-threatening infusion-related reactions associated with the administration of pertuzumab may occur.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
- Mutagenicity: Unknown
- Fertility effects: Unknown
  Pertuzumab is not recommended for use in pregnancy. Oligohydramnios, delayed fetal development and embryo/fetal death have been observed in animals.
  Adequate contraception should be used by both sexes during treatment, and for **7 months** after the last dose.
  Monitor for oligohydramnios in patients who become pregnant during pertuzumab therapy. Perform appropriate fetal testing if oligohydramnios occurs
- Excretion into breast milk: Probable
  Human IgGs are excreted into human milk; **breastfeeding** is not recommended.
- Fertility effects: Unknown

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H - Interactions

No evidence of drug-drug interaction between pertuzumab and the following drugs: Trastuzumab, paclitaxel, docetaxel, gemcitabine, erlotinib, capecitabine, carboplatin.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Cardiac assessment (physical exam and either 2D ECHO or MUGA)	Baseline, repeat every 12 weeks during treatment and every 6 months after the end of treatment until 24 months after the last dose
Infusion reactions	60 minutes after the first infusion and 30 minutes after subsequent infusions
CBC	Baseline and at each visit
Clinical toxicity assessment for infection, bleeding, neurotoxicity, hypersensitivity, fatigue, cutaneous reactions, cardiovascular, GI or respiratory effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Pertuzumab with Trastuzumab (Biosimilar) - Unresectable Locally Recurrent or Metastatic Breast Cancer

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K - References

Product Monograph: Perjeta® (pertuzumab). Hoffmann-La Roche Limited, April 2019.

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Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. Drugs. 2012 Feb 12;72(3):353-60.

O'Sullivan CC, Swain SM. Pertuzumab: evolving therapeutic strategies in the management of HER2-overexpressing breast cancer. Expert Opin Biol Ther 2013;13(5):779-90.

Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14(6):461-71.

Von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017 Jul 13;377(2):122-131.

September 2022 Updated NDFP form

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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