DRUG NAME: Atezolizumab

SYNONYM(S): MPDL3280A, RG7446, RO5541267[1]

COMMON TRADE NAME(S): TECENTRIQ®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Atezolizumab is a humanized IgG1 monoclonal antibody immune checkpoint inhibitor that binds to programmed death-ligand 1 (PD-L1) and blocks its interaction with PD-1 and B7-1 receptors on T-cells. PD-L1 is an immune checkpoint protein expressed on tumour cells and tumour-infiltrating immune cells that down regulates anti-tumour T-cell function; blocking these receptors restores anti-tumour T-cell activity.[1,2]

PHARMACOKINETICS:

Distribution	linear two-compartment disposition model	
	cross blood brain barrier?	no information found
	volume of distribution	6.9 L
	plasma protein binding	no information found
Metabolism	not defined; expected to be degraded into small peptides and amino acids via catabolic pathways (similar to endogenous IgG antibodies)	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	first-order elimination	
	urine	no information found
	feces	no information found
	terminal half life	27 days
	clearance	0.2 L/day

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Breast cancer
*Liver cancer
*Lung cancer, non-small cell
*Lung cancer, small cell

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to atezolizumab or mouse proteins[2]

Caution:
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** *prior* to starting atezolizumab due to potential interference with the efficacy of atezolizumab; corticosteroids or immunosuppressants may be used *during* treatment with atezolizumab for the management of immune-mediated adverse reactions[2]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[3-6]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, female test subjects experienced an irregular menstrual cycle pattern and an absence of fresh corpora lutea during the atezolizumab dosing phase. These changes occurred at exposures six times greater than the human therapeutic exposure and were reversible during the dose-free recovery phase. No effect was observed on testicles or semen in male subjects.[2,7,8]

Pregnancy: Atezolizumab has not been studied in pregnant women. However, endogenous IgG1 is known to cross the placental barrier, particularly during the third trimester. Therefore, as a humanized IgG1 antibody, atezolizumab is expected to be transmitted from mother to fetus. In animal models, blocking PD-L1 signalling disrupted tolerance to the fetus and resulted in increased rates of abortion and stillbirth. In addition, immune-mediated disorders were reported in the offspring of PD-1 and PD-L1 knockout mice. Women of reproductive potential should use effective contraception while on atezolizumab and continue for at least five months after treatment has been discontinued.[2,7]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should wait at least five months after the last dose of atezolizumab before breastfeeding.[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.[9,10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (6-17%, severe 2-12%)[2,11]
	leukopenia (severe 2%)
	lymphopenia (severe 14%)
	neutropenia (≥2%, severe 2%)[2,11]
	thrombocytopenia (1-3%, severe ≤2%)
cardiac	***immune-mediated myocarditis*** (severe <1%)[2,12]; see paragraph following **Side Effects** table
endocrine (see paragraph following **Side Effects** table)	***immune-mediated adrenal insufficiency*** (<1%, severe <1%)[2,7]
	immune-mediated diabetes mellitus, new onset type 1 or 2 (<1%)[2,7]; including diabetic ketoacidosis

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	immune-mediated hyperthyroidism (≤3%)
	immune-mediated hypophysitis (<1%)
	immune-mediated hypothyroidism (4-5%, severe <1%)
eye (see paragraph following **Side Effects** table)	***immune-mediated ocular inflammatory toxicity*** (<1%)[2,7]; including optic neuritis, uveitis, keratitis, retinopathy
gastrointestinal	*emetogenic potential:* low[13]
	abdominal pain (3-14%, severe ≤3%)
	colitis, immune-mediated colitis (≤1%, severe ≤1%); including ischemic colitis; see paragraph following **Side Effects** table
	constipation (7-26%)[2,11]
	dry mouth (3%)[11]
	dysphagia (≤2%, severe <1%)
	immune-mediated diarrhea (11-22%, severe ≤1%)[2,11]; see paragraph following **Side Effects** table
	immune-mediated pancreatitis (<1%); see paragraph following **Side Effects** table
	nausea (12-27%, severe ≤2%)[2,11]
	stomatitis (3%)[11]
	vomiting (6-19%, severe ≤1%)[2,11]
general disorders and administration site conditions	*extravasation hazard:* none[14]
	asthenia (7-19%, severe ≤1%)[2,11]
	chills (4-11%, severe <1%)
	edema, peripheral (9-14%)[2,11]
	fatigue (25-51%, severe 2-6%)[2,11]
	influenza-like illness (5-6%, severe <1%)[2,11]
	infusion related reaction (1%, severe <1%); see paragraph following **Side Effects** table
	pain (8-10%)[2,11]
	pyrexia (11-23%, severe ≤1%)[2,11]
hepatobiliary	***immune-mediated hepatitis*** (≤4%, severe ≤4%)[2,7]; see paragraph following **Side Effects** table
immune system	hypersensitivity (≤1%, severe <1%); including anaphylaxis
infections and infestations (see paragraph following **Side Effects** table)	***infection*** (42%, severe 11%); sometimes fatal
	pneumonia (≥4%, severe 4%)
	sepsis (severe ≥1%)
	urinary tract infection (23%, severe 7%)
investigations	alkaline phosphatase increase (severe 2-5%)
	ALT increase (3-6%, severe 1-3%)[2,11]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	AST increase (3-6%, severe ≤3%)[2,11]
	bilirubin increase (severe ≤2%)[2,7]
	creatinine increase (severe 2-3%)
	INR increase (severe 2%)
	TSH decrease (4-8%)[7]
	TSH increase (16-17%)[7]
metabolism and nutrition	appetite decrease (13-27%, severe ≤1%)[2,11]
	hypercalcemia (severe 2%)
	hyperglycemia (3-5%, severe ≤1%)
	hyperkalemia (severe 2%)
	hypoalbuminemia (severe 3-4%)
	hypoglycemia (severe 1%)
	hypokalemia (4-6%, severe ≤3%)
	hypomagnesemia (severe 1%)
	hyponatremia (4-12%, severe 2-12%)
	hypophosphatemia (≥5%, severe 2-5%)[2,11]
musculoskeletal and connective tissue	arthralgia (8-18%, severe ≤1%)[2,11]
	back pain (5-18%)[2,11]
	immune-mediated myositis, including rhabdomyolysis (<1%, severe <1%); see paragraph following **Side Effects** table
	muscle spasms (3%)[11]
	musculoskeletal pain, myalgia (6-11%, severe <1%)[2,11]
	pain in extremities (10%)
nervous system	***immune-mediated encephalitis*** (<1%); see paragraph following **Side Effects** table
	Guillain-Barre syndrome (<1%); see paragraph following **Side Effects** table
	headache (6-10%, severe <1%)[2,11]
	immune-mediated meningitis (<1%); see paragraph following **Side Effects** table
	immune-mediated myasthenic syndrome/myasthenia gravis (<1%)[2,7]; see paragraph following **Side Effects** table
	neuropathy, peripheral (3%)[11]
psychiatric	confusion (≥1%)
renal and urinary	hematuria (16%)
	immune-mediated nephritis (<1%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (10-23%)[2,11]
	dyspnea (6-20%, severe 2-3%)[2,11]
	hypoxia (2%, severe ≤1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nasal congestion (2-5%)
	pneumonitis, immune-mediated pneumonitis (1-4%, severe ≤2%)[2,7,11]; including radiation pneumonitis; see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (<1%)[11]
	dermatitis acneiform (3%)[11]
	dry skin (5%)[11]
	night sweats (4%)[11]
	pruritus (8-15%, severe <1%)
	rash, immune-mediated rash (8-18%, severe ≤1%)[2,11]; including drug eruption, palmar-plantar erythrodysesthesia; see paragraph following **Side Effects** table
vascular	hypotension (2-5%, severe <1%)[2,11]

Adapted from standard reference[2] unless specified otherwise.

Immune-mediated adverse events are a spectrum of side effects caused by general immunologic enhancement that can occur at any time during atezolizumab treatment or months after discontinuation. Consider the etiology of reported endocrinopathy, diarrhea/colitis, hepatitis, ocular toxicity, pneumonitis, rash, etc. to be immune-mediated until another etiology is confirmed. Early identification and timely intervention are important as symptoms can be severe or fatal if not recognized and treated quickly. Strongly advise patients to promptly report symptoms and to avoid self-treatment without medical advice. Management of symptoms is based on the severity of the reaction and may require treatment interruption, administration of corticosteroids, and/or supportive care. For severe symptoms, if there is no improvement within 72 hours despite steroids, consider initiating additional immunosuppressive therapy. Corticosteroids should be appropriately tapered following resolution of symptoms to grade 1 or less. Atezolizumab may be restarted if the steroid dose has been reduced to 10 mg/day or less of prednisone (or equivalent) within 12 weeks and symptoms remain controlled. Referral to appropriate medical specialty may be required to manage immune-mediated complications related to treatment. Most immune-mediated endocrinopathies can be managed by withholding atezolizumab until the patient is clinically stable and/or initiating symptomatic management as indicated (e.g., insulin, thyroid hormone replacement, etc.). ***Permanent discontinuation*** of atezolizumab should be considered for the following:

- grade 3-4: pneumonitis, hepatitis, nephritis, myocarditis, myositis (grade 4 or recurrent grade 3);
- grade 4: colitis, diarrhea, hypophysitis, pancreatitis (grade 4 or any grade recurrent), rash, other immune-mediated adverse reaction not previously listed;
- any grade: meningitis, encephalitis, myasthenic syndrome/myasthenia or Guillain-Barre syndrome;
- grade 2 or 3 reactions (excluding endocrinopathies) that do not resolve to grade 1 or less within 12 weeks.[2,15]

For further information on management of immune-mediated adverse reactions, see BC Cancer Protocol SCIMMUNE ***Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitors Immunotherapy***.

For grade 1 or 2 ***infusion related reactions***, interrupt or slow infusion rate. Consider premedication with antipyretics and antihistamines for subsequent infusions. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***. Permanently discontinue atezolizumab for grade 3 or 4 infusion related reactions.[2]

Severe infections, including sepsis, herpes encephalitis, pneumonia, and mycobacterial infection leading to retroperitoneal hemorrhage have been reported in up to 11% of patients receiving atezolizumab. Withhold atezolizumab for grade 3 or 4 infections. Atezolizumab may be restarted upon resolution of symptoms to grade 1 or less.[1,2,7]

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INTERACTIONS: no information found

SUPPLY AND STORAGE:

***Injection*:** Hoffmann-La Roche Limited supplies atezolizumab as 840 mg and 1200 mg ready-to-use, single use (preservative-free) vials in a concentration of 60 mg/mL. Refrigerate. Protect from light. Do not shake.[16]

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.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use[2]
Intermittent infusion[16-18]	***over 30-60 min*** • first infusion is given over 60 min; if tolerated, subsequent infusions can be given over 30 min[2]
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.

***Adults*:**

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

	Cycle Length:	
Intravenous:	***3 weeks***[17,19-21]:	***1200 mg IV for one dose on day 1*** (total dose per cycle 1200 mg)
	4 weeks[16,18,21]:	***1680 mg IV for one dose on day 1*** (total dose per cycle 1680 mg)

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

Cycle Length:
4 weeks[16]: 840 mg IV for one dose on day 1 and day 15 (total dose per cycle 1680 mg)

2 weeks[16,21]: 840 mg IV for one dose on day 1 (total dose per cycle 840 mg)

Concurrent radiation: no information found

Dosage in myelosuppression: no information found

Dosage in renal failure: CrCl ≥30 mL/min: no adjustment required[2]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild to moderate impairment (bilirubin ≤3 x ULN and any AST): no adjustment required[22]
severe impairment (bilirubin >3 x ULN and any AST); no information found

Dosage in dialysis: no information found

Children: safety and efficacy has not been established[2]

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