# DRUG NAME: Durvalumab

**SYNONYM(S):** MEDI 4736[1]

**COMMON TRADE NAME(S):** IMFINZI®

**CLASSIFICATION:** immunotherapy

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

## MECHANISM OF ACTION:

Durvalumab is a fully human immunoglobulin G1 kappa monoclonal antibody checkpoint inhibitor that blocks the interaction between programmed death ligand 1 (PD-L1) and programmed death 1 (PD-1) and CD80 on T-cells. PD-L1 blockade enhances antitumour immune responses and leads to increased T-cell activation and delayed tumour growth.[2,3]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Distribution | steady state at 16 weeks | |
| | cross blood brain barrier? | no information found |
| | volume of distribution | 5.6 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 | clearance decreases over time (not considered clinically relevant) | |
| | urine | no information found |
| | feces | no information found |
| | terminal half life | 17 days |
| | clearance | 8.2 mL/h |

Adapted from standard reference[2] unless specified otherwise.

## USES:

***Primary uses:***

*Biliary tract cancer
*Liver cancer[4,5]
*Lung cancer, non-small cell
*Lung cancer, small cell
*Urothelial cancer

***Other uses:***

*Health Canada approved indication



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## SPECIAL PRECAUTIONS:

***Caution:***
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** *prior* to starting durvalumab due to potential interference with the efficacy of durvalumab; corticosteroids or immunosuppressants may be used *during* treatment with durvalumab for the management of immune-mediated adverse reactions[2,6]
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[7-10]
- administer durvalumab prior to chemotherapy when given on the same day[11]

***Carcinogenicity:*** no information found

***Mutagenicity:*** no information found

***Fertility:*** In animal studies, no notable effects on male or female reproductive organs were reported.[2]

***Pregnancy:*** Durvalumab has not been studied in pregnant women. Endogenous IgG1 is known to cross the placental barrier, particularly during the third trimester. Therefore, as a humanized IgG1 antibody, durvalumab 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. Women of reproductive potential should use effective contraception while on durvalumab and for three months after treatment has been discontinued.[2]

***Breastfeeding*** is not recommended due to the potential secretion into human breast milk. In animal studies, durvalumab was detected in breast milk and was associated with premature neonatal death. Women should wait at least three months after the last dose of durvalumab 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.[12,13]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | anemia (8-47%, severe 3-12%) |
| | lymphocytopenia (43-45%, severe 11%)[2,3] |
| | neutropenia (8%, severe 1%) |
| gastrointestinal | *emetogenic potential:* low[13,14] |
| | abdominal pain (10-14%, severe <1%)[2,3] |
| | ***colitis*** (≤18%)[3] |
| | constipation (12-26%, severe ≤2%) |
| | ***diarrhea*** (17-18%, severe <1%) |
| | nausea (14-22%, severe 2%) |
| | vomiting (8-13%, severe ≤2%) |
| general disorders and administration site conditions | *extravasation hazard:* none[15] |
| | edema, peripheral (8-15%, severe 2%)[2,3] |
| | fatigue, asthenia (11-39%, severe ≤3%)[2,3] |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | infusion related reaction (1-2%, severe <1%); see paragraph following **Side Effects** table |
| | pyrexia (15-16%, severe <1%) |
| hepatobiliary | ***hepatitis*** (12%)[3]; sometimes fatal |
| immune system (see paragraph following **Side Effects** table) | adrenal insufficiency (<1%; severe <1%); median onset 141 days |
| | aseptic meningitis (<1%, severe <1%) |
| | ***colitis*** (≤2%, severe <1%); median onset 74 days |
| | diabetes mellitus, type I (<1%; severe <1%); median onset 42 days |
| | ***diarrhea*** (1-2%, severe <1%); median onset 74 days |
| | hemolytic anemia (<1%)[3] |
| | ***hepatitis*** (≤2%, severe ≤2%); median onset 70 days; has been fatal |
| | ***hyperthyroidism*** (1-8%); median onset 41 days |
| | hypophysitis/hypopituitarism (<1%; severe <1%) |
| | ***hypothyroidism*** (5-12%, severe <1%); median onset 85-107 days |
| | keratitis, uveitis (<1%)[2,3] |
| | myocarditis (<1%, severe <1%) |
| | ***myositis, polymyositis*** (<1%, severe <1%): has been fatal |
| | ***nephritis*** (≤6%, severe <1%)[2,3]; median onset 95 days |
| | pancreatitis (<1%)[16] |
| | ***pneumonitis*** (≤11%, severe ≤3%); median onset 53 days |
| | ***rash*** (1-2%, severe <1%); median onset 36-74 days |
| | thrombocytopenic purpura (<1%, severe <1%); has been fatal |
| infections and infestations (see paragraph following **Side Effects** table) | dental, oral soft tissue infection (4%) |
| | influenza (3%) |
| | ***pneumonia*** (17%, severe 7%); sometimes fatal |
| | sepsis (3%, severe 3%) |
| | thrush (3%) |
| | upper respiratory tract infections (26%, severe <1%) |
| | ***urinary tract infection*** (6-16%, severe 4%) |
| investigations | alkaline phosphatase increase (28%, severe 4%) |
| | ***ALT increase*** (8-39%, severe 1-2%) |
| | ***AST increase*** (8-36%, severe 2-4%) |
| | bilirubin increase (11%, severe 1-2%)[2,3] |
| | creatinine increase (5-33%, severe ≤2%) |
| | gamma-glutamyltransferase increase (2-24%, severe 1%)[2,3] |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | thyroid stimulating hormone decrease (32%) |
| | thyroid stimulating hormone increase (27%) |
| metabolism and nutrition | appetite decrease (14-23%, severe <1%) |
| | dehydration (≥3%, severe ≥3%)[3] |
| | hypercalcemia (15%, severe 3%) |
| | hyperglycemia (44-52%, severe 3%)[2,3] |
| | hyperkalemia (18-32%, severe 2%)[2,3] |
| | hypermagnesemia (11%, severe 4%) |
| | hypoalbuminemia (37%, severe 1%) |
| | hypocalcemia (46%)[3] |
| | hypokalemia (10%, severe 1%) |
| | hyponatremia (33-45%, severe 6-11%)[2,3] |
| musculoskeletal and connective tissue | arthralgia (11-12%, severe <1%) |
| | back pain (11-17%, severe ≤4%) |
| | musculoskeletal pain (24%)[3] |
| | myalgia (8%, severe <1%) |
| renal and urinary | ***acute kidney injury*** (5%, severe 5%) |
| | dysuria (2%) |
| respiratory, thoracic and mediastinal | cough (12-40%, severe <1%) |
| | dysphonia (4%) |
| | dyspnea (12-22%, severe 2%) |
| | ***pneumonitis*** (1-34%, severe ≤5%); sometimes fatal |
| skin and subcutaneous tissue | night sweats (2%) |
| | pruritus (6-12%) |
| | ***rash*** (14-26%, severe <1%)[2,3] |

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 durvalumab 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 (grade zero for myocarditis). Durvalumab may be restarted once the steroid dose has been reduced to 10 mg/day or less of prednisone (or equivalent) and symptoms remain controlled. Referral to appropriate medical specialty may be required to manage immune-mediated complications related to treatment. Most immune-mediated endocrinopathies



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can be managed by withholding durvalumab until the patient is clinically stable and/or initiating symptomatic management as indicated (e.g., insulin, thyroid hormone replacement, etc.). Antibiotic, antifungal, and antiviral prophylaxis can be considered for patients on long term corticosteroid treatment (e.g., oral trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jiroveci* pneumonia). Permanent discontinuation of durvalumab should be considered for the following:

- grade 3-4: pneumonitis, hepatitis, colitis, diarrhea, nephritis, myocarditis, infusion related reactions;
- grade 4: myositis/polymyositis, rash, other immune-mediated adverse reaction not previously listed;
- myositis/polymyositis that does not resolve to grade 1 or less within 30 days or if there are signs of respiratory insufficiency.[2,6]

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*.**

***Infusion related reactions*** are reported in up to 2% of patients, including rare cases of severe reactions (i.e., grade 3 or 4). Reactions may manifest as flushing, rash, itching, dizziness, chills, fever, angioedema, breathing difficulties, or back or neck pain. For grade 1 or 2 reactions, decrease the durvalumab infusion rate by 50% or temporarily interrupt the infusion until the reaction has resolved. Consider premedication 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 durvalumab for grade 3 or 4 reactions.[2,17]

Upper respiratory tract ***infection***, pneumonia, and urinary tract infection are the most commonly reported infections with durvalumab treatment. However, severe infections such as sepsis are sometimes reported. Withhold durvalumab for severe infections.[2]

**INTERACTIONS:** none known[2]

## SUPPLY AND STORAGE:

***Injection*:** AstraZeneca Canada Inc. supplies durvalumab as 120 mg and 500 mg ready-to-use, single-use (preservative free) vials in a concentration of 50 mg/mL. Refrigerate. Protect from light. Do not shake.[2]

***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 | no information found |
| ***Intermittent infusion***[18-21] | ***over 60 minutes***; administer using an 0.2 or 0.22 micron in-line filter |
| Continuous infusion | no information found |
| Intraperitoneal | no information found |
| Intrapleural | no information found |



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Revised: 1 May 2024

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

| | |
|---|---|
| Intrathecal | no information found |
| Intra-arterial | no information found |
| Intravesical | no information found |

## DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults***:

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

| | | |
|---|---|---|
| *Intravenous:* | Cycle Length:<br>***2 weeks***[18,19]: | ***10 mg/kg IV for one dose on day 1***<br>(total dose per cycle 10 mg/kg) |
| | ***2 weeks***[19,22]: | ***750 mg IV for one dose on day 1***<br>(total dose per cycle 750 mg) |
| | ***3-4 weeks***[5,20,21,23-27]: | ***20 mg/kg IV for one dose on day 1***<br>(total dose per cycle 20 mg/kg) |
| | ***3-4 weeks***[5,20,22-28]: | ***1500 mg IV for one dose on day 1***<br>(total dose per cycle 1500 mg) |
| | Dose escalation or reduction is not recommended. Temporarily withhold or permanently discontinue treatment if necessary for tolerability and/or patient safety.[2] | |
| *Concurrent radiation:* | investigational[29] | |
| *Dosage in renal failure:* | CrCl ≥30 mL/min: no adjustment required[2]<br>CrCl <30 mL/min: no information found | |
| | calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$<br>* For males N=1.23; for females N=1.04 | |
| *Dosage in hepatic failure:* | mild impairment (bilirubin ≤1.5 x ULN and any AST): no adjustment required[2]<br>moderate to severe impairment (bilirubin >1.5 x ULN and any AST): no information found | |
| *Dosage in dialysis:* | no information found | |

***Children:*** safety and efficacy not established[2]



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