**Drug Monograph**



## A - Drug Name

# nivolumab

**COMMON TRADE NAME(S):** Opdivo®

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## B - Mechanism of Action and Pharmacokinetics

Nivolumab is a human monoclonal antibody (IgG4) that binds to the PD-1 receptor on T-cells, blocking interaction with PD-L1 and PD-L2 and preventing PD-1 pathway-mediated inhibition of the tumour immune response.

| | |
|---|---|
| Distribution | Nivolumab exhibits linear pharmacokinetics in the dose range of 0.1 to 20 mg/kg. |
| Metabolism | Monoclonal antibodies are catabolised into peptides and amino acids. |
| Elimination | Nivolumab clearance increases with increasing body weight. Dosing normalized to body weight produces approximately uniform steady state drug levels.<br>Half-life (Terminal): 27 days |

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## C - Indications and Status

**Health Canada Approvals:**

- Melanoma
- Classical Hodgkin lymphoma (cHL)
- Colorectal cancer (CRC)
- Gastric cancer (GC)
- Esophageal adenocarcinoma (EAC)
- Gastroesophageal junction adenocarcinoma (GEJC)
- Esophageal squamous cell cancer (ESCC)
- Non-small cell lung cancer (NSCLC)
- Renal cell carcinoma (RCC)
- Squamous cell head and neck cancer (SCCHN)
- Malignant pleural mesothelioma (MPM)
- Urothelial carcinoma (UC)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

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## D - Adverse Effects

**Emetogenic Potential:** Minimal

**Extravasation Potential:** None

The following adverse effects occurred in ≥1% of patients from a phase III study comparing nivolumab 3 mg/kg monotherapy to ipilimumab for adjuvant melanoma. Incidences of some immune-related effects were based on nivolumab monotherapy clinical studies in various tumour types (marked with [^]). Rare or severe adverse effects from other trials are also included.

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Cardiovascular | Arrhythmia (rare) | E |
| | Cardiotoxicity (including myocarditis, pericarditis; rare) | E D |
| | Hypertension (rare) | E |
| | Venous thromboembolism (rare) | E |
| Dermatological | Alopecia (2%) | E |
| | Rash (29%) (may be severe) | E |

| | | |
|---|---|---|
| | Skin hypopigmentation (4%) (vitiligo) | E |
| Gastrointestinal | Abdominal pain (9%) | E |
| | Anorexia (4%) | E |
| | Constipation (2%) | E |
| | Diarrhea (24%) (may be severe) | E |
| | Nausea, vomiting (15%) | E |
| General | Fatigue (47%) | E |
| | Sarcoidosis (rare) | E |
| Hematological | Hemolysis (immune-mediated; rare) | E |
| | Other - histiocytic necrotizing lymphadenitis (rare, NSCLC) | E |
| | Thrombocytopenia (immune mediated; rare) | E |
| Hepatobiliary | Cholestasis (rare) | E D |
| | ↑ LFTs (8%) ^ (hepatitis <1%; may be severe) | E D |
| | Pancreatitis (rare) | E |
| | Veno-occlusive disease (rare, after allo HSCT) | E D |
| Hypersensitivity | Infusion related reaction (2%) | I E |
| Immune | Graft-versus-host disease (GVHD) (rare, nivolumab given before or after allo HSCT) | E |
| | Hemophagocytic lymphohistiocytosis (rare) | E |
| | Other - Solid organ transplant rejection (rare) | D |
| Infection | Infection (2%) | E |
| Metabolic / Endocrine | Abnormal electrolyte(s) (16%) (including changes in potassium, calcium, magnesium, sodium) | E |
| | Acidosis (metabolic) | E |
| | Adrenal insufficiency (1%) | E D |
| | Hyperglycemia (<1%) (type 1 diabetes and DKA) | E D |
| | Hyperthyroidism (or hypothyroidism; 9%)^ | E |
| | Hypoparathyroidism (rare) | E |
| | Hypopituitarism (rare)^ (also hypophysitis; rare) | E D |
| | Tumour lysis syndrome (rare) | I |
| Musculoskeletal | Musculoskeletal pain (13%) | E |
| | Other - Myasthenia gravis (rare) | E |
| | Rhabdomyolysis (also myopathy, myositis; rare) | E D |
| Nervous System | Encephalitis / aseptic meningitis (rare) | E |

| | | |
|---|---|---|
| | Guillain-Barre syndrome (rare) | E |
| | Headache (10%) | E |
| | Other - Demyelination, myasthenia, polyneuropathy (rare) | E D |
| | Peripheral neuropathy (1%) | E |
| Ophthalmic | Blurred vision (1%) | E |
| | Other - Vogt-Koyanagi-Harada syndrome (rare) | E |
| | Uveitis (rare) | E |
| Renal | Nephritis (<1%) ^ | E |
| | Nephrotoxicity (2%) (may be severe)^ | E |
| Respiratory | Cough, dyspnea (4%) | E |
| | Pneumonitis (3%) ^ | E D |
| Vascular | Vasculitis (rare) | 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)

**Refer to the CCO guideline for detailed description of Immune-mediated toxicities and their management**

The most common side effects for nivolumab include fatigue, rash, diarrhea, abnormal electrolyte(s), nausea, vomiting, musculoskeletal pain and headache.

The presentation of adverse effects may be different compared to other anti-cancer agents and early diagnosis and appropriate management are critical.

**Immune-mediated** adverse effects are more common when nivolumab is given in combination with ipilimumab compared to nivolumab monotherapy.

**Immune-mediated endocrinopathies**, including hypo or hyperthyroidism, hypophysitis, adrenal insufficiency, and diabetic ketoacidosis have been reported. The median time to onset with nivolumab monotherapy was 11 weeks.

Gastrointestinal adverse immune reactions such as **diarrhea** and/or **colitis** have been commonly reported. The median time to onset with nivolumab monotherapy was 8 weeks. **CMV infection/reactivation** has been reported in patients with immune-related colitis who are refractory to corticosteroids. Addition of an alternative immunosuppressive agent or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-related colitis, if other causes are excluded (including CMV infection/reactivation, other viral, bacterial and parasitic etiology).

**Immune-mediated hepatotoxicity** has been reported and may be severe. The median time to onset with nivolumab monotherapy was 10 weeks.

Nivolumab in combination with cabozantinib can cause higher frequencies of severe LFT elevations compared to nivolumab alone. Liver enzyme elevations after treatment discontinuation has been reported.

Severe, including fatal cases of **immune-mediated pneumonitis**, including **interstitial lung disease**, have been reported. The median time to onset with nivolumab monotherapy was 15 weeks.

**Nephrotoxicity** presents as slowly increasing creatinine, with a median onset at 12 weeks with nivolumab monotherapy. Pathology commonly shows tubule-interstitial nephritis.

**Severe rash**, including rare cases of **Steven-Johnson syndrome** (SJS) and **toxic epidermal necrolysis** (TEN), has been reported.

**Infusion reactions** are uncommon, but may be severe. Patients with mild to moderate infusion reactions may receive nivolumab with premedication and close monitoring.

**Anti-product antibodies**, including neutralizing antibodies have been found in 10% of patients on monotherapy. There was no evidence of altered pharmacokinetics or toxicity associated with anti-product antibodies. Neutralizing antibodies were not associated with loss of efficacy.

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## E - Dosing

Refer to protocol by which patient is being treated.

**Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.

Some treatment indications require a validated test to determine PD-L1 tumour status or MSI-H/dMMR status. Refer to the product monograph for details.

**Pre-medications (prophylaxis for infusion reaction):**

- Routine pre-medication is not recommended.
- May consider pre-medication with antipyretics and H1-receptor antagonists if an IR has occurred in the past.

***Adults:***

**Nivolumab monotherapy:**†

Nivolumab 3 mg/kg IV every 2 weeks

**OR**

Nivolumab 240 mg IV every 2 weeks

**OR**

Nivolumab 480 mg IV every 4 weeks

(† Health Canada approved dosing. NDFP funded dosing may differ; refer to nivolumab NDFP forms for details.)

**Combination therapy:**

Various dosing and schedules are used depending on the indication. Refer to the product monograph or related regimen monographs for details.

***Dosage with Toxicity:***

- Healthcare professionals should also consult the most recent nivolumab product monograph for additional information.
- Refer to the related product monographs or regimen monographs for dose modifications in combination therapy.
- When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld.
- Do not restart nivolumab (or nivolumab and ipilimumab) while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive drugs. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications (e.g. high-dose corticosteroids).

**Summary of Principles of Management**

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.
- Dose escalation or reduction is not recommended.
- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.
- Organ-specific system-based toxicity management is recommended.
- **Refer to the CCO guideline for detailed description of Immune-mediated toxicities and their management**

For dose modifications due to **liver enzyme elevations** during treatment with nivolumab and cabozantinib, refer the the product monographs for details.

**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 rate.<br>• Manage the symptoms.<br><br>**Restart:**<br><br>• Once symptoms have resolved, the infusion may be restarted with close monitoring. | • Re-challenge with close monitoring and pre-medications. |
| 3 or 4 | • Stop treatment.<br>• Aggressively manage symptoms. | • Discontinue permanently (do not re-challenge). |

***Dosage with Hepatic Impairment:***

| Hepatic Impairment | Nivolumab Dose |
|---|---|
| Mild (bilirubin >1 - 1.5 x ULN or AST > ULN) | No dose adjustment needed |
| Moderate (bilirubin >1.5 - 3 x ULN and any AST)<br>or<br>Severe (bilirubin >3 x ULN and any AST) | No data. Not been studied. |

Nivolumab in combination with cabozantinib has not been studied in patients with hepatic impairment; no dosing recommendation can be provided.

***Dosage with Renal Impairment:***

| Renal Impairment | Nivolumab Dose |
|---|---|
| Mild to Moderate | No dose adjustment needed. |
| Severe | Insufficient data available. |

***Dosage in the elderly:***

No overall differences in safety or efficacy were reported for patients aged ≥ 65 years compared to younger patients.

In monotherapy clinical trials, limited safety and efficacy data were available for cHL and recurrent HNSCC in patients aged ≥ 65 years. There were also limited data for metastatic RCC or NSCLC, adjuvant urothelial carcinoma or adjuvant melanoma in patients aged ≥ 75 years.

In combination therapy, data were too limited to draw conclusions from colorectal cancer patients aged ≥ 65 years. Higher rates of serious adverse reactions and/or discontinuation were observed in ESCC (with ipilimumab), metastatic NSCLC, and MPM in patients aged ≥ 75 years.

***Children:***

Safety and efficacy have not been established in pediatric patients.

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## F - Administration Guidelines

- Withdraw the required volume of nivolumab 10 mg/mL injection and aseptically transfer into a sterile IV container (PVC container, non-PVC container, or glass bottle).
- Nivolumab may be administered undiluted or diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
- If diluted, the final infusion concentration should range between 1 to 10 mg/mL. Final volume of infusion must not exceed 160 mL.
- For patients < 40 kg, the total volume of infusion must not be > 4 mL/kg of patient weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard if solution is cloudy, if there is pronounced discolouration or if there is foreign particulate matter.
- Administer by IV infusion over 30 minutes via a sterile, non-pyrogenic, low protein binding in-line filter (pore size 0.2 to 1.2 micrometer).
- Do not infuse concomitantly with other agents.
- Flush the line with normal saline or D5W after each dose.
- If given with ipilimumab OR with ipilimumab and chemotherapy, administer nivolumab first, followed on the same day by ipilimumab and then by chemotherapy. Use separate infusion bags and filters, if applicable, for each infusion.
- If nivolumab is given with cabozantinib, administer nivolumab first during the day, then cabozantinib on an empty stomach preferably in the evening.
- If a scheduled dose is missed, it should be administered as soon as possible. Adjust administration schedule to maintain the prescribed dosing interval
- Store unopened nivolumab vials in original packaging between 2$^{o}$C to 8$^{o}$C. Protect from light.

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:

- Use with caution in patients on a controlled sodium diet. Each 10 mg (= 1 mL) of nivolumab contains 0.1 mmol (2.3 mg) sodium.
- Use of a PD-1 blocking antibody with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials, due to increased mortality reported.
- Use with caution in patients with:
  - autoimmune disease
  - history of pneumonitis or interstitial lung disease or recent chest radiation
  - prior or planned allogeneic stem cell transplant
  - infection with HIV, or active coinfection with HBV/HCV or HBV/HDV as these patients were excluded from clinical trials.

### Other Drug Properties:

- Carcinogenicity: Unknown

### Pregnancy and Lactation:

- Mutagenicity: Unknown
- Fetotoxicity: Documented in animals
- Pregnancy:
  Nivolumab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **5 months** after the last dose.
- Excretion into breast milk: Probable
  Immunoglobulins are known to be secreted into breast milk; therefore as a human IgG4 antibody, there is potential for infant exposure to nivolumab via breast milk.
  Breastfeeding is not recommended during treatment, and for at least **5 months** after the last dose.
- Fertility effects: Unknown

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## H - Interactions

No formal drug interaction studies have been conducted. Nivolumab is unlikely to affect the pharmacokinetics of other drugs.

The use of systemic corticosteroids and other immunosuppressants before starting nivolumab should be avoided because of their potential interference with its activity; however, they can be used after starting nivolumab to treat immune-related adverse reactions.

Acetaminophen may affect the response to immune checkpoint inhibitors. Further clinical studies are needed to determine the exact mechanism and the appropriate clinical management (Bessede et al, 2022).

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

### **Recommended** Clinical Monitoring

| Monitor Type | Monitor Frequency |
|---|---|
| CBC | Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose |
| Liver function tests | Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose |
| Renal function tests, including electrolytes | Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose |
| Thyroid function tests | Baseline, and as clinically indicated, for at least up to 5 months after the last dose |
| Blood glucose | Baseline, and as clinically indicated, for at least up to 5 months after the last dose |

| | |
|---|---|
| Pituitary and adrenal function tests | Baseline, and as clinically indicated, especially when on physiologic replacement therapy and for at least up to 5 months after the last dose |
| Response assessment | Patients with non-squamous NSCLC or SCCHN and tumours that are PD-L1 negative or unknown status should be monitored closely for progression during the first months of treatment |
| GVHD (in patients with prior allo HSCT or those planned for allo HSCT after nivolumab discontinued)<br><br>Solid organ transplant rejection (if applicable) | As clinically indicated |
| Clinical toxicity assessment for infusion reactions, fatigue, immune-mediated reactions, including diarrhea, rash, endocrine, respiratory, musculoskeletal, neurologic, cardiac and ophthalmic effects | At each visit and for at least up to 5 months after the last dose |

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 )

- Nivolumab - Advanced Melanoma (Unresectable or Metastatic Melanoma)
- Nivolumab - Advanced or Metastatic Non-Small Cell Lung Cancer
- Nivolumab - Advanced or Metastatic Renal Cell Carcinoma and No Prior mTOR Inhibitor
- Nivolumab - Advanced or Metastatic Renal Cell Carcinoma and Prior mTOR Inhibitor
- Nivolumab - Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck which is Platinum Resistant or Refractory
- Nivolumab plus Ipilimumab - Advanced Melanoma (Unresectable or Metastatic Melanoma)
- Nivolumab - Relapsed Classical Hodgkin Lymphoma (cHL) Post-Autologous Stem Cell Transplant (ASCT) or ASCT Ineligible
- Nivolumab plus Ipilimumab - Metastatic Renal Cell Carcinoma
- Nivolumab plus Ipilimumab - Advanced Malignant Pleural Mesothelioma
- Nivolumab plus Ipilimumab - In Combination with Platinum Doublet Chemotherapy for First Line Metastatic or Recurrent Non-Small Cell Lung Cancer
- Nivolumab - First-line Treatment of Advanced Gastric, Esophageal, and Esophagogastric Junction Adenocarcinoma
- Nivolumab - Adjuvant Treatment of Completely Resected Esophageal or Esophagogastric Junction Cancer
- Nivolumab - Adjuvant Treatment of Urothelial Carcinoma
- Nivolumab - Neoadjuvant Treatment for Non-Small Cell Lung Cancer
- Nivolumab - In Combination with Cabozantinib for First Line Advanced or Metastatic Renal Cell Carcinoma
- Nivolumab - Adjuvant Treatment for Completely Resected Stage III or IV Melanoma
- Nivolumab - Adjuvant Treatment for Completely Resected Stage IIB or IIC Melanoma

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## K - References

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Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol 2017;28(8):2002-8.

Zhao X, Ivaturi V, Gopalakrishnan M, et al. Abstract CT101: A model-based exposure-response (ER) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types. Cancer Res 2017;77(13 suppl):DOI: 10.1158/1538-7445.AM2017-CT101.

**October 2024** Updated Dosage and Toxicity section and NDFP forms

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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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