

**Composition:**

**Nivamo 40mg Injection:** Each 4 ml sterile solution contains Nivolumab INN 40mg (10mg/ml)

**Nivamo 100mg Injection:** Each 10 ml sterile solution contains Nivolumab INN 100mg (10mg/ml)

**Nivamo 240mg Injection:** Each 24 ml sterile solution contains Nivolumab INN 240mg (10mg/ml)

**Pharmacology:**

**Mechanism of Action:** Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

**Indication:**

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of:

- Patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
- Patients with unresectable or metastatic melanoma, in combination with ipilimumab.
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- Patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving NIVOLUMAB.
- Patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy.
- Patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.
- Adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or more lines of systemic therapy that includes autologous HSCT.
- Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Patients with hepatocellular carcinoma who have been previously treated with sorafenib.

**Dosage and Administration:**

**Recommended Dosage for Unresectable or Metastatic Melanoma**

Single Agent: The recommended dose of NIVOLUMAB as a single agent is either: 240 mg every 2 weeks or 480 mg every 4 weeks. Administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

With Ipilimumab : The recommended dose of NIVOLUMAB is 1 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 3 mg/kg administered as an intravenous infusion over 90 minutes on the same day, every 3 weeks for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of the combination, administer NIVOLUMAB as a single agent, either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for Adjuvant Treatment of Melanoma**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year.

**Recommended Dosage for NSCLC**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for RCC**

The recommended dose of NIVOLUMAB as a single agent is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for cHL**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for SCCHN**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for Urothelial Carcinoma**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for CRC**

The recommended dose of NIVOLUMAB is 240 mg every 2 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Recommended Dosage for HCC**

The recommended dose of NIVOLUMAB is either: 240 mg every 2 weeks or 480 mg every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

**Dose Modifications**

Recommendations for NIVOLUMAB modifications are provided in below Table 1. When NIVOLUMAB is administered in combination with ipilimumab, if NIVOLUMAB is withheld, ipilimumab should also be withheld. Review the Full Prescribing Information for ipilimumab for recommended dose modifications. There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue NIVOLUMAB in patients with severe or

life-threatening infusion reactions.

**Recommended Dose Modifications for Nivolumab**

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose <sup>a</sup>
	Grade 3 diarrhea or colitis	Withhold dose a when administered as a single agent
	Grade 4 diarrhea or colitis	Permanently discontinue when administered with ipilimumab
Pneumonitis	Grade 2 pneumonitis	Withhold dose <sup>a</sup>
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC <sup>b</sup>	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose <sup>c</sup>
	If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN	
	If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Permanently discontinue
	Grade 4 hypophysitis	Withhold dose <sup>a</sup>
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose <sup>a</sup>
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose <sup>a</sup>
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose <sup>a</sup>
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose <sup>a</sup>
	Immune-mediated encephalitis	Permanently discontinue
Other	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	

\* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0

a Resume treatment when adverse reaction improves to Grade 0 or 1.

b HCC: hepatocellular carcinoma.

c Resume treatment when AST/ALT returns to baseline.

**Preparation and Administration**

Visually inspect drug product solution for particulate matter and discoloration prior to administration. NIVOLUMAB is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

**Preparation**

Withdraw the required volume of NIVOLUMAB and transfer into an intravenous container. Dilute NIVOLUMAB with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of NIVOLUMAB.

**Administration**

Administer the infusion over 30 minutes through an intravenous line containing a sterile,

non-pyrogenic, low protein binding in-line filter. Do not co-administer other drugs through the same intravenous line.

**Storage of Infusion**

The product does not contain a preservative. After preparation, store the NIVOLUMAB infusion either: at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

**Contraindications: None**

**Warnings and Precautions:**

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis.
- Immune-mediated colitis: Withhold NIVOLUMAB when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold NIVOLUMAB when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis.
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation.
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia.
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation.
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash.
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis.
- Infusion reactions: Discontinue NIVOLUMAB for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.
- Complications of allogeneic HSCT after NIVOLUMAB: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

**Adverse Reactions**

Most common adverse reactions (≥20%) in patients were:

- NIVOLUMAB as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain.
- NIVOLUMAB with ipilimumab for melanoma: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea.
- NIVOLUMAB with ipilimumab for renal cell carcinoma: fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite.

**Use In Specific Populations**

**Pregnancy:** Based on its mechanism of action and data from animal studies, NIVOLUMAB can cause fetal harm when administered to a pregnant woman. The effects of NIVOLUMAB are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

**Lactation:** It is not known whether NIVOLUMAB is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NIVOLUMAB, advise women to discontinue breastfeeding during treatment with NIVOLUMAB.

**Females and Males of Reproductive Potential**

**Contraception:** Based on its mechanism of action, NIVOLUMAB can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with NIVOLUMAB and for at least 5 months following the last dose of NIVOLUMAB.

**Pediatric Use:** The safety and effectiveness of NIVOLUMAB have not been established in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or in pediatric patients less than 18 years old for the other approved indications.

**Geriatric Use:** No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported.

**Drug Interactions**

No formal pharmacokinetic drug-drug interaction studies have been conducted with Nivolumab.

**Overdose:**

There is no information on overdose with Nivolumab

**Storage:**

Store vials under refrigeration at 2° C- 8°C (36° F- 46°F) in original carton to protect from light. Do not freeze or shake. Keep out of the reach of children.

**Commercial Packaging:**

Nivamo 40mg Injection: Each commercial box contains 1 vial of 4ml solution  
Nivamo 100mg Injection: Each commercial box contains 1 vial of 10ml solution  
Nivamo 240mg Injection: Each commercial box contains 1 vial of 24ml solution

Manufactured by:



**Ziska Pharmaceuticals Ltd.**

Kaliakoir, Gazipur, Bangladesh