BEACON® Pharmaceuticals Limited

LF29901

IV Infusion

NIVOMAB

Nivolumab Injection

Injection for single use only

COMPOSITION

Nivomab 40 Injection: Each 4 mL contains Nivolumab INN 40 mg (10 mg/mL)

Nivomab 100 Injection: Each 10 mL contains Nivolumab INN 100 mg (10 mg/mL)

THERAPEUTIC CLASS: Anti-cancer

CLINICAL PHARMACOLOGY

Mode 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

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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.

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Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent Nivolumab and Nivolumab with Ipilimumab.

Nivolumab as a single agent: The PK of single-agent Nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of Nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in

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patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady-state. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of Nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to Nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of Nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Nivolumab with Ipilimumab: When Nivolumab 1 mg/kg was administered in combination with Ipilimumab 3 mg/kg, the CL of Nivolumab was

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increased by 29%, and the CL of Ipilimumab was unchanged compared to Nivolumab administered alone. When Nivolumab 3 mg/kg was administered in combination with Ipilimumab 1 mg/kg, the CL of Nivolumab and Ipilimumab were unchanged. When administered in combination, the CL of Nivolumab increased by 20% in the presence of anti-Nivolumab antibodies and the CL of Ipilimumab was unchanged in presence of anti-Ipilimumab antibodies.

INDICATIONS

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

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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 metastatic small cell lung cancer with progression after platinum based chemotherapy and at least one other line of therapy.

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- 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 3 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:
  - Have disease progression during or following platinum-containing chemotherapy

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  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment
- 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, as a single agent or in combination with Ipilimumab.
- Patients with locally advanced or metastatic urothelial carcinoma who with platinum-containing chemotherapy
- Patients with hepatocellular carcinoma who have been previously treated with Sorafenib.

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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

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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

As an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. Review the Prescribing Information for Ipilimumab for additional information prior to initiation.

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

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recurrence or unacceptable toxicity for up to 1 year.

Recommended Dosage for Metastatic 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 Small Cell Lung Cancer

The recommended dose of Nivolumab:
- 240 mg every 2 weeks

Recommended Dosage for Advanced RCC

Single Agent

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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 3 mg/kg administered as an intravenous infusion over 30 minutes, followed by Ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses. 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

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As an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. Review the Prescribing Information for Ipilimumab prior to initiation.

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 Locally Advanced or Metastatic SCCHN

The recommended dose of Nivolumab is either:
- 240 mg every 2 weeks or

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- 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 MSI-H/dMMR CRC

Single Agent

The recommended dose of Nivolumab as a single agent is 240 mg every 2

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weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

With Ipilimumab

The recommended dose of Nivolumab is 3 mg/kg administered as an intravenous infusion over 30 minutes, followed by Ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer

Nivolumab 240 mg as a single agent every 2 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

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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 Table 1. When Nivolumab is administered in combination with Ipilimumab, if Nivolumab is withheld, Ipilimumab should also be withheld. Review the Prescribing Information for Ipilimumab for recommended dose modifications.

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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.

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.

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Table 1: Recommended Dose Modifications for Nivolumab

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
		Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with Ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue

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Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/ non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) morethan 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[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue

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Hepatitis/HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • 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	Withhold dose[c]

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	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	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal Insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue

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Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected StevensJohnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severeneurologic signs or symptoms	Withhold dose[a]

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	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

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* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4); [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
- 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.
- For adult and pediatric patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.

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- Discard partially used vials or empty vials of Nivolumab.

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.

Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size

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of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

When administered in combination with Ipilimumab, infuse Nivolumab first followed by Ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

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

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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

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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 graftversus-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.

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- ***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.
- Most common adverse reactions (=20%) with Nivolumab in combination with Ipilimumab are fatigue, rash, diarrhea, nausea, pyrexia, musculoskeletal pain, pruritus, abdominal pain, vomiting, cough, arthralgia, decreased appetite, dyspnea.

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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.

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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 (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) 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.

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Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment.

Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild or moderate hepatic impairment. Nivolumab has not been studied in patients with severe hepatic impairment.

DRUG INTERACTIONS

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

OVERDOSAGE

There is no information on overdosage with Nivolumab.

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PHARMACEUTICAL INFORMATION

Storage Condition

Store the vial in original carton at 2°C to 8°C. Protect from light. Do not freeze or shake. Discard unused portion. Keep out of the reach of children.

Presentation and Packaging

Nivomab 40 Injection: Each commercial box contains 1 vial of 4 mL solution

Nivomab 100 Injection: Each commercial box contains 1 vial of 10 mL solution

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