OPDIVO®

(nivolumab)
Concentrate for solution for infusion

Risk Minimisation Information for Healthcare Professionals
Guide for Prescribing

OPDIVO® is indicated for the treatment of different types of tumours, as monotherapy or in combination with ipilimumab.

For a complete list of the current authorised indications and the type of patients in which you should use nivolumab with caution, please refer to the nivolumab Summary of Product Characteristics (SmPC).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via email:

postlicensing.medicinesauthority@gov.mt

Adverse reactions should also be reported to Bristol-Myers Squibb Medical Information at 00 356 23976333 or **pv@ammangion.com**

Bristol-Myers Squibb

This Guide

- Is provided for healthcare professionals (HCPs) who are involved in the treatment of patients on nivolumab, with or without other medicinal products.
- Is essential to ensure the safe and effective use of nivolumab and appropriate management of some related adverse reactions.
- Is to be read before prescribing and administering nivolumab.
- Introduces the Patient Alert Card. It is important to review the Patient Alert Card with patients before each treatment cycle and at each visit, in order to reinforce their understanding of side effects and the need to contact a HCP if they develop side effects.

Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to all HCPs involved in their treatment. You can obtain a Patient Alert Card at *AM Mangion Ltd, Mangion Building, New Street off Valletta Road, Luqa, LQA6000 - Malta*

What is Nivolumab?[1]

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[1]

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in selected approved indications as specified in the SmPC.

When nivolumab is administered in combination with ipilimumab, refer to the SmPC for ipilimumab prior to initiation of treatment.

Before prescribing nivolumab you should check:

- Liver function tests.
  Nivolumab must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe (total bilirubin > 3 × ULN with any AST) hepatic impairment
- Signs and symptoms of electrolyte disturbance, dehydration, endocrinopathies, hyperglycaemia, and changes in thyroid function
- If the patient is allergic to the active substance or to any of the excipients
- If the patient is taking systemic corticosteroids and other immunosuppressants at baseline before starting nivolumab
- If the patient has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents
- If the patient is going to drive or operate machinery
- If the patient is pregnant or planning to become pregnant, or if the patient is breast-feeding
- If the patient belongs to any special population group in which caution is required, including where there is limited or absent data[1]

Summary of Important Information

- Nivolumab, as monotherapy or in combination with ipilimumab, increases the risk of severe immune-related adverse reactions (irARs), which can include pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin reactions, and other irARs (see details later), as well as potential complications of allogeneic haematopoietic stem cell transplant (HSCT) in classical Hodgkin Lymphoma (cHL). These irARs can occur several months after the last dose of nivolumab.
- Early diagnosis and appropriate management of adverse events are essential to minimise life-threatening complications.
- Suspected adverse reactions must be promptly evaluated to exclude infectious or other alternate aetiologies.
- Based on the severity of the irAR, the treatment should be withheld or discontinued and systemic corticosteroid therapy may be required. Upon improvement, treatment may be resumed after corticosteroid taper[1]; treatment must be permanently discontinued for any severe irAR that recurs and for any life-threatening irAR.[1]
- Patients and caregivers should be informed about the symptoms of irARs and the importance of reporting them immediately to the treating physician. A Patient Alert Card must be given to patients at any visit, and may support the discussion about risks.
- Patients should be advised to carry the Patient Alert Card at all times and to show it to all HCPs involved in their treatment.

Early Diagnosis and Appropriate Management

- Prompt recognition of adverse events and appropriate treatment are essential to minimise life-threatening complications.[1]
- Corticosteroids with or without additional immunosuppressive therapy may be required for the management of severe irARs. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least one month duration should be initiated upon improvement[1], as rapid tapering may lead to worsening or recurrence of the adverse reaction[1]. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.[1]
- Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.[1]
- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.
- Please refer to the nivolumab SmPC (and ipilimumab SmPC if you are using combination therapy) for guidelines on treatment. When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either nivolumab monotherapy or the combination treatment may be resumed based on the evaluation of the individual patient.[1]
- In addition to the treatment modifications in the following tables, treatment with nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for[1]:
  - Any Grade 3 irAR that recurs
  - Any Grade 4 irAR
  - At first onset of Grade 3 irARs: pneumonitis, diarrhoea/colitis (combination treatment only), elevation in AST/ALT/bilirubin, adrenal insufficiency, or myocarditis
  - Any Grade 2 or 3 irAR that persists despite treatment modification
  - Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day

Immune-Related Adverse Reactions and Treatment Modifications

Immune-related adverse reaction	Severity	Recommended treatment (nivolumab or nivolumab + ipilimumab) modification
Pneumonitis (radiographic changes like focal ground glass opacities or patchy filtrates, dyspnoea, hypoxia)	Grade 2 pneumonitis	Withhold treatment. Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment. Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.
Colitis (diarrhoea, abdominal pain, mucus or blood in stool)	Grade 2 diarrhoea or colitis	Withhold treatment. If persistent, manage with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.
	Grade 3 diarrhoea or colitis (nivolumab monotherapy only)	Withhold treatment. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued.
	Grade 3 (combination therapy only) or Grade 4 (monotherapy and combination) diarrhoea or colitis	Permanently discontinue treatment. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
Hepatitis (transaminase or total bilirubin elevations)	Grade 2 elevation in transaminase or total bilirubin	Withhold treatment. Persistent elevations in laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.
	Grade 3 or 4 elevations in transaminase or total bilirubin	Permanently discontinue treatment. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
Skin (rash, pruritus, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN])	Grade 3 rash	Withhold treatment until symptoms resolve. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents
	Grade 4 rash	Permanently discontinue treatment. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
	SJS or TEN	If suspected SJS or TEN, withhold treatment and refer the patient to a specialised unit for assessment and treatment. If the patient has confirmed SJS or TEN then permanently discontinue treatment.

Grade definition according to NCI CTCAE v.4					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental Activity Daily Living (ADL)	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Hepatobiliary disorders	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
ALT/AST increase	> ULN-3.0 ×ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN	
Bilirubin increase	> ULN-1.5 × ULN	> 1.5-3.0 × ULN	> 3.0-10.0 × ULN	> 10.0 × ULN	
Stevens-Johnson syndrome			Skin sloughing covering <10% Body Surface Area (BSA) with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10-30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Rash acneiform	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Toxic Epidermal Necrolysis				Skin sloughing covering ≥30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death

Immune-Related Adverse Reactions and Treatment Modifications

Immune-related adverse reaction	Severity	Recommended treatment (nivolumab or nivolumab + ipilimumab) modification	
Nephritis and Renal Dysfunction (asymptomatic increase of serum creatinine)	Grade 2 or 3 serum creatinine elevation	Withhold treatment. Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and treatment must be permanently discontinued.	
	Grade 4 serum creatinine elevation	Permanently discontinue treatment. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.	
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency including secondary adrenocortical insufficiency, hypophysitis including hypopituitarism, diabetes, diabetic ketoacidosis)	Grade 2 or 3 hypothyroidism	Withhold treatment	Initiate thyroid hormone replacement as needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.
	Grade 4 hypothyroidism	Permanently discontinue treatment	
	Grade 2 or 3 hyperthyroidism	Withhold treatment	Initiate antithyroid medication as needed. Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents if acute inflammation of the thyroid is suspected. Upon improvement (of Grade 2 or 3 events), treatment may be resumed after corticosteroid taper, if needed.
	Grade 4 hyperthyroidism	Permanently discontinue treatment	
	Grade 2 adrenal insufficiency	Withhold treatment	Physiologic corticosteroid replacement should be initiated as needed. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue treatment	
	Grade 2 or 3 hypophysitis	Withhold treatment	Initiate hormone replacement as needed. Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents if acute inflammation of the pituitary gland is suspected. Upon improvement (of Grade 2 or 3 events), treatment may be resumed after corticosteroid taper, if needed. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.
	Grade 4 hypophysitis	Permanently discontinue treatment	
	Grade 3 diabetes	Withhold treatment	Initiate insulin replacement as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised.
	Grade 4 diabetes	Permanently discontinue treatment	

Grade definition according to NCI CTCAE v.4					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	> 1-1.5 × baseline; >ULN-1.5 × ULN	> 1.5-3.0 × baseline; >1.5-3.0 × ULN	> 3.0 baseline; > 3.0-6.0 × ULN	> 6.0 × ULN	
Renal and urinary disorders	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypophysitis (endocrine disorders general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diabetes mellitus (hyperglycaemia)	Fasting glucose value > ULN-160 mg/dL; Fasting glucose value > ULN-8.9 mmol/L	Fasting glucose value >160-250 mg/dL; Fasting glucose value > 8.9-13.9 mmol/L	> 250-500 mg/dL; >13.9-27.8 mmol/L; hospitalisation indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences	Death
Acidosis	pH < normal, but ≥ 7.3		pH < 7.3	Life-threatening consequences	Death

Other Immune-Related Adverse Reactions

The following irARs were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types[1]:

- Pancreatitis
- Uveitis
- Demyelination
- Autoimmune neuropathy (including facial and abducens nerve paresis)
- Guillain-Barré syndrome
- Myasthenic syndrome
- Encephalitis
- Gastritis
- Sarcoidosis
- Duodenitis

- ❖ Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued and appropriate treatment instituted.
- ❖ Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing.
- ❖ Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma (cHL)

Preliminary results from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant related mortality. Until further data become available, careful consideration to the potential benefits of allogeneic HSCT and the possible increased risk of transplant related complications should be made case-by-case.

In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients.

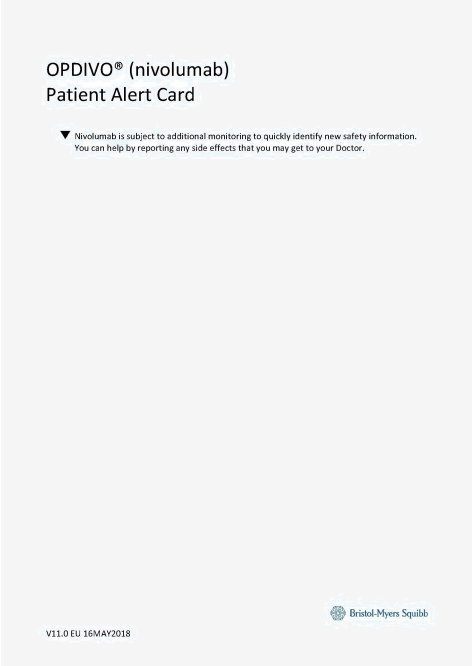
Infusion Reactions

Adverse reaction	Severity	Recommended treatment (nivolumab or nivolumab + ipilimumab) modification
Infusion reactions	Mild or moderate infusion reaction	Closely monitor administration of treatment and use premedication according to local treatment guidelines for prophylaxis of infusion reactions.
	Severe or life-threatening infusion reaction	Treatment must be discontinued and appropriate medical therapy administered.

Patient Alert Card

It is important that you distribute the Patient Alert Card to any patient receiving nivolumab or nivolumab in combination with ipilimumab for the first time and at each visit. You can use the Patient Alert Card to discuss treatment and the related risks.

This educational material is designed to help patients understand their treatment and how to act should they experience adverse reactions. You should complete your contact details in the Patient Alert Card and advise the patient to carry it at all times.


OPDIVO® (nivolumab)
Patient Alert Card

▼ Nivolumab is subject to additional monitoring to quickly identify new safety information.
You can help by reporting any side effects that you may get to your Doctor.

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Checklist for Patient's Visit (First or Following)

FIRST VISIT

- Discuss the treatment with the patient, fill in the Patient Alert Card, and advise the patient to carry it at all times
- Tell the patient not to treat their own symptoms and to seek immediate medical attention should any adverse reaction occur or worsen
- Inform the patient that they may experience growth of existing tumours or develop new tumours, and that this does not necessarily mean that the treatment is ineffective
- Make the appropriate checks (see page 2 of this guide and the SmPC)
- Check for signs and symptoms of conditions that are in the *Warnings and Precautions* or *Contraindications* sections of the SmPC

ANY FOLLOWING VISIT

- Make the appropriate checks (see page 2 of this guide and the SmPC)
- Remind the patient not to treat their own symptoms
- Remind the patient to contact you immediately should they experience an adverse reaction, even if mild
- Remind the patient that early diagnosis and appropriate management are essential to minimise the severity of adverse reactions and their associated complications

All healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

By Mail:	Malta Medicines Authority Sir Temi Żammit Buildings Malta Life Sciences Park San Ġwann SĠN 3000
By Phone:	00356 23439000
By Fax:	00356 23439161
By Email:	**postlicensing.medicinesauthority@gov.mt**

If you require any further information regarding the use of nivolumab or nivolumab in combination with ipilimumab, please contact the Bristol-Myers Squibb Medical Information department at *00 356 2397 6505*

References:

1. OPDIVO Summary of Product Characteristics.