OPDIVO (nivolumab)® + YERVOY (ipilimumab)® Prescribing Information

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OPDIVO® (NIVOLUMAB) PRESCRIBING INFORMATION

United Kingdom

Consult Summary of Product Characteristics (SmPC) before prescribing.

This prescribing information also contains information on the use of nivolumab in combination with YERVOY (ipilimumab) or cabozantinib, or chemotherapy, or in combination with ipilimumab and chemotherapy, as relevant in combination therapy. If prescribing nivolumab in combination with cabozantinib or ipilimumab, please also consult the cabozantinib or ipilimumab SmPC.

Presentation:

- Vials of 10 mg/mL nivolumab concentrate for solution for infusion.

Indications:

As monotherapy	In adults and adolescents ≥12 years (Y) of age: ▪ Advanced (unresectable or metastatic) melanoma. Relative to nivolumab monotherapy, an increase in progression free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD L1 expression. ▪ Adjuvant treatment with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. In adults: ▪ Locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. ▪ Advanced renal cell carcinoma (RCC) after prior therapy. ▪ Relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. ▪ Recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) in patients progressing on or after platinum-based therapy. ▪ Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy. ▪ Adjuvant treatment of completely resected oesophageal or gastro-oesophageal junction (GOJ) cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy ▪ Adjuvant treatment of muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.
In combination with ipilimumab	In adults and adolescents ≥12Y: ▪ Advanced (unresectable or metastatic) melanoma In adults: ▪ First line treatment of unresectable malignant pleural mesothelioma (MPM) ▪ First-line treatment for intermediate/ poor-risk advanced RCC ▪ Treatment of mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (CRC) after prior fluoropyrimidine-based combination chemotherapy. ▪ First-line treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.
In combination with ipilimumab and chemotherapy	In adults: First-line treatment of metastatic NSCLC whose tumours have no sensitising EGFR mutation or ALK translocation.
In combination with chemotherapy	In adults: ▪ First-line treatment of HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5. ▪ First-line treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1% ▪ The neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) non-small cell lung cancer ▪ First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC)
In combination with cabozantinib	In adults: First-line treatment of advanced renal cell carcinoma

Dosage and administration:

PD-L1 testing:

If specified in the indication, patient selection for treatment with nivolumab based on the tumour expression of PD-L1 should be confirmed by a validated test (see SmPC sections 4.1, 4.4, and 5.1). **Nivolumab as monotherapy:** 240 mg every 2 weeks over 30 minutes intravenously (IV). For melanoma (advanced and adjuvant treatment for adults and adolescents ≥12Y weighing ≥50 kg), RCC and MIUC (adjuvant treatment): Nivolumab can also be administered at 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma) IV. For melanoma (advanced and adjuvant treatment for adolescents ≥12Y weighing <50 kg), only: Nivolumab can be administered at 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes. For adjuvant treatment of oesophageal or gastro-oesophageal junction cancer: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes. Refer to section 4.2 of SmPC for full details. Treatment with nivolumab as monotherapy should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Adjuvant treatment duration for up to 12 months. **Nivolumab in combination with ipilimumab**: Induction phase for advanced melanoma (adults and adolescents ≥12Y weighing ≥50 kg or <50 kg): 1 mg/kg nivolumab IV over 30 minutes + 3 mg/kg ipilimumab IV over 30 minutes every 3 weeks for the first 4 doses. Refer to section 4.2 of SmPC for full details. Induction phase for RCC and dMMR or MSI-H CRC: 3 mg/kg nivolumab IV over 30 minutes + 1 mg/kg ipilimumab IV over 30 minutes every 3 weeks for the first 4 doses. Maintenance phase for advanced melanoma (adults and adolescents ≥12Y weighing ≥50 kg), RCC and dMMR or MSI-H CRC: Nivolumab monotherapy IV at either 240 mg every 2 weeks over 30 minutes (3 weeks after last dose of induction phase) or for advanced melanoma and RCC only: 480 mg every 4 weeks over 60 minutes (6 weeks after last dose of induction phase). Maintenance phase for advanced melanoma (adolescents ≥12Y weighing <50 kg): Nivolumab monotherapy IV at either 3 mg/kg every 2 weeks over 30 minutes (3 weeks after last dose of induction phase) or 6 mg/kg every 4 weeks over 60 minutes (6 weeks after last dose of induction phase). Refer to section 4.2 of SmPC for full details. For MPM: 360 mg nivolumab IV over 30 minutes every

3 weeks + 1 mg/kg ipilimumab IV over 30 minutes every 6 weeks). Treatment is continued for up to 24 months in patients without disease progression. Refer to section 4.2 of SmPC for full details. For OSCC: 3 mg/kg nivolumab IV every 2 weeks or 360 mg nivolumab IV every 3 weeks over 30 minutes + 1 mg/kg ipilimumab IV over 30 minutes every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. **Nivolumab in combination with ipilimumab and chemotherapy**: For metastatic NSCLC: 360 mg nivolumab IV over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab IV over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab IV every 3 weeks in combination with 1 mg/kg ipilimumab IV every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Refer to section 4.2 of SmPC for full details. **Nivolumab in combination with chemotherapy**: For Gastric, gastrooesophageal junction or oesophageal adenocarcinoma: 360 mg IV over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks or 240 mg IV over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see SmPC section 5.1). For OSCC: 240 mg nivolumab IV every 2 weeks or 480 mg nivolumab IV every 4 weeks over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. For neoadjuvant NSCLC: 360 mg nivolumab IV over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles. For first-line treatment of unresectable or metastatic UC: 360 mg nivolumab IV over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy at either 240 mg every 2 weeks or 480 mg every 4 weeks administered IV over 30 minutes (see SmPC section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. **Nivolumab in combination with cabozantinib:** For RCC: 240 mg IV every 2 weeks over 30 minutes or 480 mg IV every 4 weeks over 60 minutes in combination with 40 mg cabozantinib administered orally every day. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity.
Administration: Instructions on dilution and handling, refer to SmPC section 4.2

Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in SmPC.

Special warnings and precautions:

Immune-related adverse reactions have occurred at higher frequencies with nivolumab in combination with ipilimumab than with nivolumab monotherapy. Similar reactions have occurred when nivolumab was administered in combination with cabozantinib relative to nivolumab monotherapy. Most adverse reactions improve or resolve with appropriate management, including corticosteroids and treatment modification. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse events including pulmonary embolism have also been reported with combination therapy. Monitor patients for cardiac and pulmonary adverse reactions continuously, plus clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration before and during treatment. Discontinue nivolumab in combination with ipilimumab for life threatening or recurrent severe cardiac and pulmonary adverse reactions. Monitor patients 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. *Immune-related pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, endocrinopathies, hyperglycaemia and changes in thyroid function:* Monitor patients for signs and symptoms. Cytomegalovirus (CMV) infection/reactivation* has been reported in patients with corticosteroid-refractory immune-related colitis. Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Patients may present with mental status changes*, unusual bowel habits*, and hypotension*. please refer to SmPC for further details. *Complications of allogeneic haematopoietic stem cell transplant (HSCT) in cHL*
Transplant related mortality* (TRM) have been observed from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab. *Immune-related skin adverse reactions:* Monitor patients for rash, including Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN). Use caution when considering nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents. *Other immune-related adverse reactions (reported in less than 1% of patients in clinical trials):*
Nivolumab as monotherapy or in combination with ipilimumab: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis and myelitis. Cases of Vogt-Koyanagi Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing. If a patient develops signs and symptoms of myotoxicity (myositis, myocarditis, and rhabdomyolysis), 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 (Refer to SmPC section 4.2) and appropriate treatment instituted. 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. Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated. Refer to SmPC section 4.4 for further information and for specific management guidelines for immune related adverse reactions. *Infusion reactions:* Severe infusion reactions have been reported. *Disease-specific precautions:* In the absence of data in some population sub-groups nivolumab or nivolumab combinations should be used with caution after careful consideration of the potential benefit/risk on an individual basis. Physicians should consider the delayed onset of nivolumab effect before initiating treatment in some tumour types in patients with rapidly progressive disease. Please refer to SmPC section 4.4. 'Disease-specific precautions' for more details. *Patients on controlled sodium diet*: Please refer to SmPC section 4.4. *Traceability:* In order to improve the traceability of biological medicinal products, the name and the

batch number of the administered product should be clearly recorded.

**asterisk denotes serious adverse drug reactions, including those that are potentially fatal or life-threatening*

Pregnancy and lactation:

Nivolumab is not recommended during pregnancy and in women of child-bearing potential not using effective contraception unless clinical benefit outweighs potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab. It is unknown whether nivolumab is secreted in human milk.

Undesirable effects*:*

Nivolumab monotherapy: *Very Common (≥ 1/10)*: upper respiratory tract infection, lymphopaenia*, anaemia, leucopoenia*, neutropaenia*, thrombocytopaenia*, decreased appetite, hyperglycaemia*, headache*, dyspnoea*, cough, diarrhoea*, vomiting, nausea, abdominal pain*, constipation, rash*, pruritus, musculoskeletal pain, arthralgia, fatigue*, pyrexia, increased aspartate aminotransferase (AST)*/ alkaline phosphatase (ALP)*/ alanine aminotransferase (ALT)*/ creatinine*/ lipase*/ amylase*, hyponatraemia*, hypoalbuminaemia*, hyperkalaemia*, hypocalcaemia*, hypomagnesaemia*, hypokalaemia*, hypercalcaemia*. *Common (≥ 1/100 to < 1/10):* infusion related reaction (including cytokine release syndrome)*, pneumonia*, bronchitis, hypersensitivity (including anaphylactic reaction)*, hypoglycaemia*, hypothyroidism*, thyroiditis, dehydration*, hyperthyroidism*, peripheral neuropathy, dizziness, oedema, blurred vision, dry eye, tachycardia, atrial fibrillation, hypertension, pneumonitis*, pleural effusion, colitis*, stomatitis, dry mouth, vitiligo, dry skin, erythema, alopecia, arthritis, renal failure (including acute kidney injury)*, increased total bilirubin*, hypermagnesaemia*, hypernatraemia*, weight decreased, pain, chest pain. *Uncommon (≥ 1/1,000 to < 1/100):* sarcoidosis*, adrenal insufficiency*, hypopituitarism*, hypophysitis*, diabetes mellitus*, autoimmune neuropathy (including facial and abducens nerve paresis)*, uveitis*, myocarditis*, pancreatitis*, gastritis*, hepatitis*. *Rare (≥ 1/10,000 to < 1/1,000):* aseptic meningitis*, diabetic ketoacidosis*, hypoparathyroidism*, Guillain-Barré syndrome*, demyelination*, myasthenic syndrome*, encephalitis*, myositis (including polymyositis)*, rhabdomyolysis*, TEN*, SJS*, cystitis noninfective*. *Not known:* haemophagocytic lymphohistiocytosis*, solid organ transplant rejection*, Vogt-Koyanagi-Harada syndrome*, interstitial lung disease*. nephritis*, renal dysfunction*, multi-organ failure*, Complications of allogeneic haematopoietic stem cell transplant (HSCT) in classical Hodgkin lymphoma*, graft-versus-host-disease*, hepatic veno-occlusive disease*, myelitis (including transverse myelitis)*. **Nivolumab in combination with Ipilimumab (with or without chemotherapy):** *Very Common (≥ 1/10)*: upper respiratory tract infection, anaemia*, thrombocytopaenia*, leucopoenia*, lymphopaenia*, neutropaenia*, hypothyroidism*, decreased appetite, hyperglycaemia*, hypoglycaemia*, headache*, dizziness, cough, dyspnoea*, diarrhoea*, vomiting, nausea, abdominal pain*, constipation, rash*, pruritus, musculoskeletal pain, arthralgia, fatigue*, pyrexia, oedema (including peripheral oedema), increased ALP*/ AST*/ ALT*/ total bilirubin*/ creatinine*/ amylase*/ lipase*, hyponatraemia*, hyperkalaemia*, hypokalaemia*, hypercalcaemia*, hypocalcaemia*. *Common (≥ 1/100 to < 1/10):* pneumonia, bronchitis, conjunctivitis, eosinophilia, infusion related reaction (including cytokine release syndrome)*, hypersensitivity*, hyperthyroidism*, thyroiditis, adrenal insufficiency*, hypophysitis*, hypopituitarism*, diabetes mellitus*, dehydration*, hypoalbuminaemia, hypophosphataemia, weight decreased, peripheral neuropathy, blurred vision, dry eye, tachycardia, atrial fibrillation, hypertension, pneumonitis*, pulmonary embolism*, pleural effusion, colitis*, pancreatitis*, stomatitis, gastritis*, dry mouth, hepatitis*, alopecia, vitiligo, urticaria, dry skin, erythema, muscle spasms, muscular weakness, arthritis, renal failure (including acute kidney injury)*, chest pain, pain, chills, hypernatraemia*, hypermagnesaemia*, increased thyroid stimulating hormone, increased gamma-glutamyltransferase*. *Uncommon (≥ 1/1,000 to < 1/100)*: diabetic ketoacidosis*, autoimmune neuropathy (including facial and abducens nerve paresis)*, encephalitis*, myasthenia gravis*, uveitis*, myocarditis*, arrhythmia (including ventricular arrhythmia)*, duodenitis*, SJS*, myositis (including polymyositis)*, nephritis*. *Rare (≥ 1/10,000 to < 1/1,000):* aseptic meningitis*, sarcoidosis*, hypoparathyroidism*, Guillain-Barré syndrome*, Vogt-Koyanagi-Harada syndrome*, intestinal perforation*, TEN*, rhabdomyolysis*, cystitis noninfective*, myelitis (including transverse myelitis)*. *Not known:* haemophagocytic lymphohistiocytosis*, solid organ transplant rejection*, interstitial lung disease*, renal dysfunction*. **Nivolumab in combination with chemotherapy:** *Very Common (≥ 1/10):* neutropaenia*, anaemia*, leucopoenia*, lymphopaenia*, thrombocytopaenia*, decreased appetite, hypoalbuminaemia, hyperglycaemia*, hypoglycaemia*, peripheral neuropathy, cough, diarrhoea*, stomatitis, vomiting, nausea, abdominal pain*, constipation, rash*, musculoskeletal pain, fatigue*, pyrexia, oedema (including peripheral oedema), hypocalcaemia*, increased AST*/ALT*/ amylase*/ ALP*/ creatinine*/ lipase*/ total bilirubin*, hyponatraemia*, hypomagnesaemia*, hypokalaemia*, hyperkalaemia*, pruritus. *Common (≥ 1/100 to < 1/10):* upper respiratory tract infection, pneumonia*, febrile neutropaenia*, hypersensitivity (including anaphylactic reaction)*, infusion related reaction (including cytokine release syndrome)*, hypothyroidism*, hyperthyroidism*, hypophosphataemia, paraesthesia, dizziness, headache*, dry eye, blurred vision, tachycardia, atrial fibrillation, thrombosis*, hypertension, vasculitis, pneumonitis*, dyspnoea*, colitis*, dry mouth, palmar-plantar erythrodysaesthaesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema, arthralgia, muscular weakness, renal failure*, malaise, hypernatraemia*, hypercalcaemia*, hypermagnesaemia*, diabetes mellitus*. *Uncommon (≥ 1/1,000 to < 1/100):* adrenal insufficiency*, hypopituitarism*,uveitis*, myocarditis*, pancreatitis*, hepatitis*, cystitis noninfective*, hypophysitis*, nephritis*. *Rare (≥ 1/10,000 to < 1/1,000):* Guillain-Barré syndrome*, encephalitis*. *Not known:* interstitial lung disease*, diabetic ketoacidosis*, renal dysfunction*, TEN*, SJS*, myelitis (including transverse myelitis)*. **Nivolumab in combination with cabozantinib:** *Very Common (≥ 1/10):* upper respiratory tract infection, anaemia, thrombocytopaenia*, leucopoenia*, lymphopaenia*, neutropaenia*, hypothyroidism*, hyperthyroidism*, decreased appetite, hypoglycaemia*, hyperglycaemia*, weight decreased, dysgeusia, dizziness, headache*, hypertension, dysphonia, dyspnoea*, cough, diarrhoea*, vomiting, nausea, constipation, stomatitis, abdominal pain*, dyspepsia, palmar-plantar erythrodysaesthesia syndrome, rash*, pruritus, musculoskeletal pain, arthralgia, muscle spasm, proteinuria, fatigue*, pyrexia, oedema, increased ALP*/ ALT*/ AST*/ total bilirubin*/ creatinine*/ amylase*/ lipase*, hypokalaemia*, hypomagnesaemia*, hyponatraemia*, hypocalcaemia*, hypercalcaemia*, hypophosphataemia*, hyperkalaemia*, hypermagnesaemia*, hypernatraemia,. *Common (≥ 1/100 to < 1/10):* pneumonia, eosinophilia, hypersensitivity (including anaphylactic reaction), adrenal insufficiency*, dehydration*, peripheral

neuropathy, tinnitus, dry eye, blurred vision, atrial fibrillation, tachycardia, thrombosis, pneumonitis*, pulmonary embolism*, pleural effusion, epistaxis, colitis*, gastritis*, oral pain, dry mouth, haemorrhoids, hepatitis*, alopecia, dry skin, erythema, hair colour change, arthritis, renal failure, acute kidney injury, pain, chest pain, blood cholesterol increased, hypertriglyceridaemia. *Uncommon (≥ 1/1,000 to < 1/100)*: hypophysitis*, encephalitis autoimmune*, Guillain-Barré syndrome*, myasthenic syndrome*, uveitis*, myocarditis*, pancreatitis*, small intestine perforation*, nephritis*, infusion related hypersensitivity reaction*. *Rare (≥ 1/10,000 to < 1/1,000)*: cystitis noninfective*. *Not known:* renal dysfunction*, immune mediated nephritis*, interstitial lung disease*, TEN*, SJS*.
*asterisk denotes serious adverse drug reactions, including those that are potentially fatal or life-threatening

Prescribers should consult the SmPC in relation to other adverse reactions.

Legal category:
Nivolumab: POM. Ipilimumab: POM.

Marketing authorisation numbers and NHS list price for Opdivo:
Nivolumab 40 mg / 4mL 1 vial (PLGB 15105/0133) £439.00;
Nivolumab 100 mg / 10mL 1 vial (PLGB 15105/0133) £1,097.00;
Nivolumab 120 mg / 12mL 1 vial (PLGB 15105/0133) £1,317.00;
Nivolumab 240 mg / 24 mL 1 vial (PLGB 15105/0133) £2,633.00.

Marketing authorisation numbers and NHS list price for Yervoy:
Ipilimumab: 50 mg / 10 ml vial (PLGB 15105/0151) £3,750;
Ipilimumab: 200 mg / 40 ml vial (PLGB 15105/0151) £15,000.

Marketing authorisation holder:
Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland.

For further information contact:
medical.information@bms.com or 0800 731 1736.

Date of preparation: December 2024

Approval code: 1506-GB-2400277

Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Bristol-Myers Squibb via medical.information@bms.com or 0800 731 1736.

YERVOY® (IPILIMUMAB) PRESCRIBING INFORMATION

United Kingdom

Consult Summary of Product Characteristics (SmPC) before prescribing.

This prescribing information also contains information on the use of ipilimumab in combination with OPDIVO (nivolumab) for melanoma, as relevant in combination therapy. If prescribing ipilimumab in combination with nivolumab, please also consult the nivolumab SmPC.

Presentation:

- Ipilimumab 5 mg/ml concentrate for solution for infusion.

Indications:

- **As monotherapy or in combination with nivolumab:** Advanced (unresectable or metastatic) melanoma in adults and adolescents ≥12 years of age (≥12Y). Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (refer to SmPC sections 4.4 and 5.1).

Dosage and administration:

DOSAGE

Ipilimumab as monotherapy: For adults and adolescents ≥12Y: 3 mg/kg intravenously (I.V.) over 30 minutes every 3 weeks for a total of 4 doses.

Ipilimumab in combination with nivolumab for Melanoma: 3 mg/kg ipilimumab I.V. over 30 minutes in combination with 1 mg/kg nivolumab I.V. over 30 minutes every 3 weeks for the first 4 doses. For adults and adolescents ≥12Y weighing ≥50 kg: this is followed by nivolumab monotherapy I.V. at either 240 mg every 2 weeks (over 30 minutes) or 480 mg every 4 weeks (over 60 minutes). For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination phase if using 240 mg every 2 weeks or, 6 weeks after the last dose of the combination phase if using 480 mg every 4 weeks. For adolescents ≥12Y weighing <50 kg: This is followed by nivolumab monotherapy I.V. at either 3 mg/kg every 2 weeks (over 30 minutes) or 6 mg/kg every 4 weeks (over 60 minutes). For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination phase if using 3 mg/kg every 2 weeks or, 6 weeks after the last dose of the combination phase if using 6 mg/kg every 4 weeks (see SmPC section 4.2).Liver function tests and thyroid function tests should be evaluated at baseline and before each treatment dose.

ADMINISTRATION

Instructions on dilution and handling, refer to SmPC section 4.2

Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1.

Special warnings and precautions:

Ipilimumab as monotherapy: Ipilimumab is associated with inflammatory adverse reactions (ARs) resulting from increased or excessive immune activity (irARs). These can be severe or life-threatening and may involve gastrointestinal (including unusual bowel habits*, bloody stool*), liver, skin, nervous, endocrine (including adrenal crisis*) or other organ systems. Post marketing cases of cytomegalovirus (CMV) infection/reactivation* have been reported with corticosteroid refractory immune related colitis. Signs and symptoms of irARs, including increased stool frequency*, muscle weakness*, motor neuropathy*, sensory neuropathy* must be assessed. While most immune-related adverse reactions occurred during the induction period, onset months after the last dose of ipilimumab has also been reported. Early diagnosis and appropriate management are essential to minimise life-threatening complications. Ipilimumab should be avoided in patients with severe active autoimmune disease. Caution should be used in a patient who has previously experienced a severe or life-threatening skin AR on a prior cancer immune stimulatory therapy. Fatalities due to gastrointestinal perforation, hepatic failure, toxic epidermal necrolysis* (TEN) including Steven Johnson Syndrome* (SJS) and Guillain-Barré syndrome* (GBS) have been reported in clinical trials. Severe infusion reactions have been reported in clinical trials. Cases of Vogt-Koyanagi-Harada syndrome*, serous retinal detachment*, and cystitis noninfective* have been reported post-marketing. Transient vision loss* has been reported in patients with ipilimumab-related ocular inflammations*. Concurrent administration with vemurafenib is not recommended. Use with caution when ipilimumab is administered following prior vemurafenib. Solid organ transplant rejection* has been reported in the post marketing setting. Treatment with ipilimumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with ipilimumab versus the risk of possible organ rejection should be considered in these patients. Haemophagocytic lymphohistiocytosis (HLH) has been observed with ipilimumab as monotherapy and ipilimumab in combination with a PD 1 or PD L1 inhibitor (including with nivolumab). Use with caution. If HLH is confirmed, treatment should be discontinued and treatment for HLH initiated. Refer to SmPC section 4.4 for further information and for specific management guidelines for irARs. *Patients on controlled sodium diet:* Refer to SmPC section 4.4.

For Melanoma: Patients with ocular melanoma were excluded from clinical trials.

Ipilimumab in combination with nivolumab: Cardiac and pulmonary ARs including pulmonary embolism have been reported. Monitor patients for cardiac and pulmonary ARs continuously, plus clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration before and during treatment. Discontinue ipilimumab in combination with nivolumab for life-threatening or recurrent severe cardiac and pulmonary ARs. Monitor patients continuously (at least up to 5 months after the last dose) as an AR may occur at any time during or after discontinuation of therapy. Most irARs improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications. *Immune-related colitis, pneumonitis, hepatitis, nephritis, renal dysfunction, endocrinopathies, neurological reactions, gastrointestinal reactions*: Monitor patients for signs and symptoms. *Immune-related skin ARs:* Monitor patients for rash*, including SJS* or TEN*. Use caution when considering the use of ipilimumab or ipilimumab in combination with nivolumab in a patient who has previously experienced a severe or life-threatening skin AR on a prior cancer immune stimulatory therapy. Refer to SmPC for further info. *Other irARs:* pancreatitis*, uveitis*, demyelination*, autoimmune neuropathy (including facial and abducens nerve paresis)*, GBS*, myasthenia gravis*, myasthenic syndrome*, aseptic meningitis*, encephalitis*, gastritis*, duodenitis*, sarcoidosis*, myositis*, myocarditis*, rhabdomyolysis* and myelitis*. Cases of Vogt-Koyanagi-Harada syndrome*, serous retinal detachment* and cystitis noninfective* have been reported post-marketing. Transient vision loss* has been reported in patients with ipilimumab-related ocular inflammations*, please see SmPC for full details on adverse reactions. If a patient develops signs and symptoms of myotoxicity (myositis*, myocarditis*, and rhabdomyolysis*), close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity,

ipilimumab in combination with nivolumab should be withheld or discontinued (refer to SmPC section 4.2) and appropriate treatment instituted. *Infusion reactions:* Severe infusion reactions* have been reported. Melanoma patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials. For melanoma patients with rapidly progressing disease, consider the delayed onset effect before initiating treatment. Refer to SmPC section 4.4. for further information and for specific management guidelines for irARs. For additional information on warnings associated with nivolumab treatment, please refer to the nivolumab SmPC. *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. *In paediatric:* Limited, but no long-term, safety data is available on the use of Ipilimumab in adolescents ≥12Y. Ipilimumab should not be used in children younger than 12 years of age.

***** *asterisk denotes serious adverse drug reaction, including those that are potentially fatal or life-threatening*

Pregnancy and lactation:

Not recommended during pregnancy or in women of child-bearing potential not using effective contraception. It is unknown whether ipilimumab is secreted in human milk.

Undesirable effects*:*

Ipilimumab as monotherapy: *Very Common (≥ 1/10):* diarrhoea*, abdominal pain*, rash*, pruritus*, fatigue*, decreased appetite, vomiting, nausea, constipation, musculoskeletal pain, injection site reaction, pyrexia, oedema, pain. *Common (≥ 1/100 to < 1/10):* sepsis*, hypopituitarism (including hypophysitis)*, hypothyroidism*, dehydration*, peripheral sensory neuropathy*, headache*, cranial neuropathy*, peripheral neuropathy*, arrhythmia*, hypotension*, dyspnoea*, colitis*, mucosal inflammation*, abnormal hepatic function*, renal failure*, increased alanine aminotransferase (ALT)* / aspartate aminotransferase (AST)* / blood alkaline phosphatase* / blood bilirubin* / lipase*, urinary tract infection, respiratory tract infection, tumour pain, anaemia, lymphopenia, thrombocytopenia, neutropenia, hypokalemia, weight decreased, hyponatremia, confusional state, depression, dizziness, lethargy, brain oedema, blurred vision, eye pain, atrial fibrillation, flushing, hot flush, cough, allergic rhinitis, gastrointestinal haemorrhage, gastroesophageal reflux disease, gastroenteritis, stomatitis, dermatitis, erythema, vitiligo, urticaria, eczema, alopecia, night sweats, dry skin, arthralgia, myalgia, muscle spasms, arthritis, chills, asthenia, influenza-like illness. *Uncommon (≥ 1/1,000 to < 1/100):* septic shock*, haemolytic anaemia*, eosinophilia*, adrenal insufficiency*, secondary adrenocortical insufficiency*, hyperthyroidism*, mental status changes*, Guillain Barré syndrome*, meningitis (aseptic)*, autoimmune central neuropathy (encephalitis)*, uveitis*, reduced visual acuity*, iritis*, angiopathy*, acute respiratory distress* syndrome*, pneumonitis*, gastrointestinal perforation*, large intestine perforation*, intestinal perforation*, peritonitis*, pancreatitis*, hepatic failure*, hepatitis*, toxic epidermal necrolysis (including Stevens-Johnson Syndrome)*, myositis*, glomerulonephritis*, autoimmune nephritis*, renal tubular acidosis*, cystitis noninfective*, multi-organ failure*, infusion related reaction*, increased gamma-glutamyltransferase*, increased blood creatinine*, increased blood amylase*. *Rare (≥ 1/10,000 to < 1/1,000):* type 1 diabetes mellitus (including diabetic ketoacidosis)*, myasthenia gravis*, Vogt-Koyanagi-Harada syndrome*, serous retinal detachment*, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*. *Very rare (< 1/10,000):* anaphylactic reaction*. *Not known:* haemophagocytic lymphohistiocytosis*, solid organ transplant rejection*, myocarditis*, autoimmune hepatitis*, autoimmune pancreatitis*, episcleritis*, infectious peritonitis*, sarcoidosis*, hepatotoxicity*, neurological reactions*, gastrointestinal reactions*, hyperglycemia*, Myasthenia gravis-like symptoms*, myelitis*. **Ipilimumab in combination with nivolumab (with or without chemotherapy):** *Very Common (≥ 1/10):* anaemia*, thrombocytopaenia*, leucopoenia*, lymphopaenia*, neutropaenia*, hypothyroidism*, hyperglycaemia*, headache*, dyspnoea*, diarrhoea*, abdominal pain*, rash*, fatigue*, increased alkaline phosphatase* / AST* / ALT* / total bilirubin* / creatinine* / amylase* / lipase*, hyponatraemia*, hyperkalaemia*, hypokalaemia*, hypercalcaemia*, hypocalcaemia*, pruritus, upper respiratory tract infection, decreased appetite, hypoglycaemia*, dizziness, cough, vomiting, nausea, constipation, musculoskeletal pain, arthralgia, pyrexia, oedema (including peripheral oedema). *Common (≥ 1/100 to < 1/10):* infusion-related reaction (including cytokine release syndrome)*, hypersensitivity*, hyperthyroidism*, adrenal insufficiency*, hypophysitis*, hypopituitarism*, diabetes mellitus*, dehydration*, pneumonitis*, pulmonary embolism*, colitis*, pancreatitis*, gastritis*, hepatitis*, renal failure (including acute kidney injury)*, hypernatraemia*, hypermagnesaemia*, increased gamma-glutamyltransferase*, eosinophilia, peripheral neuropathy, pneumonia, bronchitis, conjunctivitis, thyroiditis, hypoalbuminaemia, hypophosphataemia, weight decreased, blurred vision, dry eye, tachycardia, atrial fibrillation, hypertension, pleural effusion, stomatitis, dry mouth, alopecia, vitiligo, urticaria, dry skin, erythema, muscle spasms, muscular weakness, arthritis, chest pain, pain, chills, increased thyroid stimulating hormone. *Uncommon (≥ 1/1,000 to < 1/100):* febrile neutropaenia*, diabetic ketoacidosis*, polyneuropathy*, autoimmune neuropathy (including facial and abducens nerve paresis)*, encephalitis*, myasthenia gravis*, uveitis*, episcleritis*, myocarditis*, arrhythmia (including ventricular arrhythmia)*, duodenitis*, Stevens-Johnson syndrome*, myositis (including polymyositis)*, nephritis*. *Rare (≥ 1/10,000 to < 1/1,000):* aseptic meningitis*, sarcoidosis*, Guillain-Barré syndrome*, Vogt-Koyanagi-Harada syndrome*, serous retinal detachment*, intestinal perforation*, toxic epidermal necrolysis*, rhabdomyolysis*, cystitis noninfective*, myelitis (including transverse myelitis)*. *Not known:* haemophagocytic lymphohistiocytosis*, solid organ transplant rejection*, renal dysfunction*, interstitial lung disease*. Refer to SmPC for all other adverse events.

***** *asterisk denotes serious adverse drug reaction, including those that are potentially fatal or life-threatening*

Prescribers should consult the SmPC in relation to other adverse reactions.

Legal category:

Ipilimumab: POM. Nivolumab: POM

Marketing authorisation numbers and NHS list price for Yervoy:

Ipilimumab 50 mg / 10 ml vial (PLGB 15105/0151) £3,750;
Ipilimumab 200 mg / 40 ml vial (PLGB 15105/0151) £15,000.

Marketing authorisation numbers and NHS list price for Opdivo:

Nivolumab 40 mg / 4mL 1 vial (PLGB 15105/0133) £439.00;
Nivolumab 100 mg / 10mL 1 vial (PLGB 15105/0133) £1,097.00;
Nivolumab 120 mg / 12mL 1 vial (PLGB 15105/0133) £1,317.00;
Nivolumab 240 mg / 24 mL 1 vial (PLGB 15105/0133) £2,633.00.

Marketing authorisation holder

Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland.

For further information contact:
medical.information@bms.com or 0800 731 1736.

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Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Bristol-Myers Squibb via medical.information@bms.com or 0800 731 1736.