Consult summary of product characteristics (SmPC) prior to prescribing and for full list of adverse events

PRESENTATION: 10 mg/mL concentrate for solution for infusion. Available in 2 vial sizes 4 mL (contains 40 mg nivolumab) and 10 mL (contains 100 mg nivolumab). INDICATION: For the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. DOSAGE: Adults: The recommended dose is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Administration: The total dose of Nivolumab BMS required can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. It must not be administered as an intravenous push or bolus injection. Refer to the SmPC for instructions on handling and administration of the product. Dose escalation or reduction is not recommended. Permanent discontinuation of treatment or withholding of doses: Dosing delay or discontinuation may be required based on individual safety and tolerability, refer to the SmPC. CHILDREN: Safety and efficacy in children under 18 years of age have not been established. Elderly: No dose adjustment is required for elderly patients. Renal impairment: No dose adjustment is required for patients with mild hepatic impairment. Nivolumab BMS must be administered with caution in patients with moderate (total bilirubin >1.5 × 3 to the upper limit of normal [ULN]) and any aspartate amino transferase (AST) or severe (total bilirubin >3 × ULN and any AST) hepatic impairment. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC. WARNINGS AND PRECAUTIONS: Nivolumab BMS is contraindicated in patients with active or recent cutaneous or non-cutaneous immunological reactions that are not related to the treatment. Nivolumab BMS should be administered under the care of a specialist in hematology and oncology. Adverse events should also be reported to Bristol-Myers Squibb Medical Information on 0800 731 1736 or medical.information@bms.com.
Consult summary of product characteristics (SmPC) prior to prescribing and for full list of adverse events.

**PRESENTATION:** 10 mg/mL concentrate for solution for infusion. Available in 2 vial sizes 4 mL (contains 40 mg nivolumab) and 10 mL (contains 100 mg nivolumab). A vial contains 100 mg or 300 mg nivolumab (contains 200 mg or 600 mg nivolumab as a mono-clonal antibody to an intracellular domain of programmed death receptor 1 (PD-1)).

**ADOPTION:** The total dose of Opdivo required can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. It must not be administered as an intravenous push or bolus injection. Refer to SmPC for instructions on handling and administration of the product. Dose escalation or reduction is not recommended. Permanent discontinuation of treatment or withholding of doses: Dosing delay or discontinuation may be required based on individual safety and tolerability, refer to the SmPC. Children: Safety and efficacy in children below 18 years of age have not been established. Elderly: No dose adjustment is required for elderly patients. Renal impairment: No dose adjustment in mild to moderate renal impairment. Hepatic impairment: No dose adjustment required in patients with mild hepatic impairment. Opdivo must be administered with caution in patients with moderate (total bilirubin > 1.5 to 3 × the upper limit of normal [ULN]) and any aspartate amino transferase (AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

**WARNINGS AND PRECAUTIONS:** Opdivo is associated with immune-related adverse reactions. Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with Opdivo may occur at any time during or after discontinuation of Opdivo therapy. For suspected immune related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, Opdivo should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Opdivo 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. Opdivo must be permanently discontinued for any severe immune related adverse reaction that recurs and for any life threatening immune related adverse reaction. Physicians should consider the delayed onset of Opdivo effect before initiating treatment in patients with rapidly progressing disease (Refer to SmPC). Immune-related pneumonitis: Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed. Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy infiltrates), dyspnea, and hypoxia. Immune-related colitis: Severe diarrhoea or colitis has been observed. Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Immune-related hepatitis: Severe hepatitis has been observed. Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Immune-related nephritis or renal dysfunction: Severe renal failure or renal dysfunction has been observed patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic proteinuria. Immune-related endocrinopathies: Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetes ketoacidosis have been observed. Monitor patients for clinical signs and symptoms of endocrinopathies and for changes in thyroid function. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related. Immune-related rash: Severe rash has been observed in patients treated with Opdivo. Adverse events due to rash include facial oedema, periorbital oedema, non-life threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents. Other immune-related adverse reactions: The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abdomens nerve paresis), Guillain-Barré syndrome, hypopituitarism, and myasthenic syndrome. Infusion reactions:Severe infusion reactions have been reported. Special populations: Patients with a baseline performance score ≥ 2, active brain metastases, ocular melanoma, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials. In the absence of data, Opdivo should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis. Experience with Opdivo in previously untreated BRAF mutation-positive melanoma is limited. Patients on controlled sodium diet: Each mL contains 0.1 mmol (or 2.5 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet. DRUG INTERACTIONS: Opdivo is not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of Opdivo. The use of systemic corticosteroids and other immunosuppressants should be avoided before starting Opdivo. However, systemic corticosteroids and other immunosuppressants can be used after Opdivo to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting Opdivo treatment does not appear to preclude the response on Opdivo. FERTILITY, PREGNANCY AND LACTATION: Fertility: Studies to evaluate the effect of Opdivo on fertility have not been performed. The effect of Opdivo on male and female fertility is unknown. Pregnancy: Not recommended during pregnancy and in women of child-bearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of Opdivo. Breast-feeding: It is unknown whether Opdivo is secreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue from Opdivo therapy. UNDESIRABLE EFFECTS: Very Common (≥ 1/10): diarrhoea, nausea, rash, pruritus, fatigue, increased AST, increased ALT, total bilirubin, increased alkaline phosphatase, increased creatinine, lymphopenia, thrombocytopenia, anaemia. Common (1/100 to < 1/10): upper respiratory tract infection, infusion related reaction, hypothyroidism, hyperglycaemia, hyponatraemia, decreased appetite, peripheral neuropathy, headache, dizziness, hypertension, paresthesia, dyspnea, cough, colitis, stomatitis, vomiting, abdominal pain, constipation, vitiligo, dry skin, erythema, alopecia, musculoskeletal pain, arthralgia, pyrexia, oedema (including peripheral oedema), increased lipase, increased amylase, neutropenia, Uncommon (1/1,000 to < 1/100): anaphylactic reaction, hypersensitivity, adrenal insufficiency, hypopituitarism, hypothyroidism, hyperglycaemia, diabetes ketoacidosis, diabetes mellitus, Guillain-Barré syndrome, demyelination, myasthenic syndrome, autoimmune neuropathy (including facial and abdomens nerve paresis), uveitis, arthrythmia (including ventricular arrhythmia), pancreatitis, erythema multiforme, pruritis, rosacea, tubulointestinal nephritis, renal failure. Please refer to the SmPC for further details.

LEGAL CATEGORY: POM. MARKETING AUTHORISATION NUMBER AND BASIC NHS PRICE: 40 mg / 4 mL 1 vial (EU/15/1014401) £439.00; 100 mg / 10 mL 1 vial (EU/15/1014402) £1,097.00 MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EIEG, Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH. Tel: 0800-730-1736. DATE OF PREPARATION: June 2015 1506U1500105-01

Adverse events should be reported. Reporting forms and information can be found at http://mhra.gov.uk/yellowcard.

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