Kyprolis®▼ (carfilzomib) Brief Prescribing Information
Please refer to the Summary of Product Characteristics (SmPC) before prescribing Kyprolis. **Pharmaceutical Form:** Powder for solution for infusion presented as a single use vial. **Indication:** Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. **Dosage and Administration:** Intravenous (iv) infusion on two consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15 and 16), followed by a 12 day rest period. Each 28-day period is considered one treatment cycle. Kyprolis in combination with lenalidomide and dexamethasone: Infuse over 10 minutes at a starting dose of 20mg/m^2 (max dose 44mg) on days 1 & 2 of cycle 1. If tolerated, increase dose to 27mg/m^2 (max dose 60mg) on day 8 of cycle 1. From cycle 13, omit doses on day 8 & 9 of each cycle. In combination with Kyprolis, lenalidomide is administered as 25 mg orally on days 1–21 and dexamethasone is administered as 40 mg orally or iv on days 1, 8, 15, and 22 of the 28 day cycles. Continue treatment until disease progression or until unacceptable toxicity occurs; treatment beyond 18 cycles should be based on an individual benefit:risk assessment as data are limited. Consider appropriate dose reduction for lenalidomide according to the current lenalidomide SmPC. Kyprolis in combination with dexamethasone: Infuse over 30 minutes at a starting dose of 20 mg/m^2 (max dose 44 mg) on days 1 and 2 of cycle 1. If tolerated, increase dose to 56 mg/m^2 (max dose 123 mg) on day 8 of cycle 1. Dexamethasone is administered as 20 mg orally or iv on days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28 day cycles. Continue treatment until disease progression or until unacceptable toxicity occurs. Modify dosing based on haematologic, renal and other non-haematologic toxicity as defined in the SmPC. Consider antiviral prophylaxis in patients treated with Kyprolis to decrease the risk of herpes zoster reactivation. Monitor platelet counts frequently. Thromboprophylaxis is recommended based on an individual benefit:risk assessment. Adequate hydration is required before Kyprolis administration in cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity, give additional fluids after Kyprolis administration in cycle 1 as needed. Monitor all patients for evidence of volume overload and tailor fluid requirements to individual patient needs. Monitor serum potassium monthly or more frequently as clinically indicated. Assess renal function at treatment initiation and monitor at least monthly, particularly in patients with lower baseline creatinine clearance (CrCL < 30 mL/min) for whom there are limited efficacy and safety data. Assess liver enzymes and bilirubin at treatment initiation and monitor monthly during treatment, regardless of baseline values; pay special attention to patients with moderate and severe hepatic impairment for whom there are very limited efficacy and safety data. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; women who are breast-feeding. Refer to relevant SmPC for contraindications, special warnings and precautions for products used in combination with Kyprolis. **Special Warnings and Precautions:** For patients who experience grade 3 or 4 cardiac events or dyspnoea, or pulmonary toxicities/hypertension or hypertensive crisis, stop Kyprolis until recovery and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment. Cardiac disorders: New or worsening cardiac failure, myocardial ischaemia and infarction have occurred, including fatal outcomes. The risk of cardiac failure is increased in elderly (≥ 75 years) and Asian patients. A thorough assessment for cardiovascular risk factors prior to starting treatment is recommended. Patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction (in the last 4 months), and in patients with uncontrolled angina or arrhythmias should have a comprehensive cardiological assessment prior to starting treatment. Electrocardiographic changes: An effect of Kyprolis on QT interval prolongation cannot be excluded. Pulmonary toxicity: Acute respiratory distress syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred, some events have been fatal. Pulmonary hypertension: Pulmonary hypertension has been reported, some events have been fatal. Dyspnoea: Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Hypertension: Hypertension, including hypertensive crisis and hypertensive emergency, has been observed, some events have been fatal. Control hypertension prior to starting and during treatment. Evaluate all patients for hypertension during treatment. If hypertension cannot be controlled, reduce dose. Acute renal failure: Cases of acute renal failure have been reported, some of these events have been fatal. Tumour lysis syndrome (TLS): Cases of TLS, including with fatal outcome, have been reported. Consider patients with a high tumour burden at greater risk. Ensure patients are well hydrated before Kyprolis administration in cycle 1 and subsequent cycles as needed. Consider uric acid lowering medicinal products in patients at high risk for TLS. Monitor for evidence of TLS during treatment. Stop Kyprolis until TLS is resolved. Infusion reactions: Infusion reactions, including life-threatening reactions, have been reported in patients who received Kyprolis. Reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Dexamethasone should be administered prior to Kyprolis to reduce the incidence and severity of reactions. Haemorrhage and thrombocytopenia: Haemorrhage, often associated with thrombocytopenia has been reported; some events have been fatal. Venous thromboembolic events: Events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported. Closely monitor patients with known risk factors for thromboembolism, minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia), and administer other agents that may increase the risk of thrombosis with caution (e.g. erythropoietic agents or

hormone replacement therapy). Hepatic toxicity: Cases of hepatic failure, including fatal cases, have been reported. Thrombotic microangiopathy: Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported, some events have been fatal. Monitor for signs and symptoms of TTP/HUS and stop treatment if suspected. Once excluded, Kyprolis can be restarted. The safety of reinitiating Kyprolis in patients previously experiencing TTP/HUS is unknown. Posterior reversible encephalopathy syndrome (PRES): Cases of PRES have been reported. Kyprolis should be discontinued if PRES is suspected. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known. Hepatitis B Virus (HBV) reactivation: Cases of HBV reactivation have been reported. Patients should be screened for HBV before initiation of treatment. For patients with positive HBV serology, consider prophylaxis with antivirals. Monitor for clinical and laboratory signs of HBV reactivation during and after the end of treatment. The safety of resuming carfilzomib after HBV is adequately controlled is not known. Resumption of therapy should be discussed with experts in managing HBV. Progressive Multifocal Leukoencephalopathy (PML): Cases of PML have been reported in patients receiving carfilzomib who have had prior or concurrent immunosuppressive therapy. Patients should be monitored for any new of worsening neurological, cognitive or behavioural signs and symptoms that may be suggestive of PML. If PML is suspected, further administration must be suspended until PML has been excluded by a specialist with appropriate diagnostic testing. If PML is confirmed, carfilzomib must be discontinued. Contraception: Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. Kyprolis may decrease the efficacy or oral contraceptives. Patients using oral contraceptives or hormonal contraception associated with a risk of thrombosis should switch to an alternative method. Male patients must use effective contraception measures during and for 3 months following treatment if their partner is pregnant or of childbearing potential not using effective contraception. Sodium content: Kyprolis contains 0.3mmol (7mg) of sodium per mL of reconstituted solution. **Interactions:** Caution should be observed when carfilzomib is combined with medicinal products that are substrates of CYP1A2, 2C8, 2C9, 2C19 and 2B6 (e.g. oral contraceptives), or with substrates of P-gp (e.g. digoxin, colchicine). **Fertility, pregnancy and lactation:** No available data on use of Kyprolis in pregnant women; should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Breast-feeding is contra-indicated during and for at least 2 days after treatment with Kyprolis. No fertility studies have been performed. **Undesirable Effects:** Adverse reactions in patients receiving Kyprolis: very common (≥ 1/10) pneumonia, respiratory tract infection, thrombocytopenia, neutropenia, anaemia, lymphopenia, leukopenia, hypokalaemia, hyperglycaemia, decreased appetite, insomnia, dizziness, peripheral neuropathy, headache, hypertension, dyspnoea, cough, vomiting, diarrhoea, constipation, abdominal pain, nausea, back pain, arthralgia, pain in extremity, muscle spasms, increased blood creatinine, pyrexia, peripheral oedema, asthenia, fatigue, chills; common (≥ 1/100 to < 1/10) sepsis, lung infection, influenza, herpes zoster, urinary tract infection, bronchitis, gastroenteritis, viral infection, nasopharyngitis, rhinitis, febrile neutropenia, dehydration, hyperkalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypocalcaemia, hypophosphataemia, hyperuricaemia, hypoalbuminaemia, anxiety, confusional state, paraesthesia, hypoaesthesia, cataract, blurred vision, tinnitus, cardiac failure, myocardial infarction, atrial fibrillation, tachycardia, ejection fraction decreased, palpitations, deep vein thrombosis, hypotension, flushing, pulmonary embolism, pulmonary oedema, epistaxis, oropharyngeal pain, dysphonia, wheezing, pulmonary hypertension, gastrointestinal haemorrhage, dyspepsia, toothache, increased alanine aminotransferase, increased aspartate aminotransferase, increased gammaglutamyltransferase, hyperbilirubinaemia, rash, pruritus, erythema, hyperhidrosis, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, muscular weakness, acute kidney injury, renal failure, renal impairment, decreased creatinine renal clearance, chest pain, pain, infusion site reactions, influenza-like illness, malaise, increased c-reactive protein, increased blood uric acid, infusion related reaction; uncommon (≥ 1/1,000 to < 1/100) clostridium difficile colitis, cytomegalovirus infection, hepatitis B virus reactivation, drug hypersensitivity, HUS, tumour lysis syndrome, intracranial haemorrhage, cerebrovascular accident, cardiac arrest, myocardial ischaemia, pericarditis, pericardial effusion, hypertensive crisis, haemorrhage, ARDS, acute respiratory failure, pulmonary haemorrhage, interstitial lung disease, pneumonitis, gastrointestinal perforation, hepatic failure, cholestasis, multi-organ dysfunction syndrome. Please consult the Summary of Product Characteristics for a full description of adverse reactions. **Pharmaceutical Precautions:** Do not mix or administer as an infusion with other medicinal products. Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in original carton to protect from light. Reconstitute with sterile water for injections. Reconstituted solutions in the vial, syringe, or intravenous bag may be stored at 2°C – 8°C for up to 24 hours or at 25°C for up to 4 hours. Inspect visually before administration; do not administer if any discoloration or particulate matter is observed. **Legal Category:** POM. **Presentation, Basic Costs and Marketing Authorisation Number:** Kyprolis 60mg: Pack of 1: £1,056; EU/1/15/1060/001. Kyprolis 30 mg: Pack of 1: £528; EU/1/15/1060/003. Kyprolis 10mg: Pack of 1: £176; EU/1/15/1060/002. **Marketing Authorisation Holder:** Amgen Europe B.V., Minervum 7061, NL-4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 240 Cambridge Science Park, Milton Road, Cambridge, CB4 0WD. Kyprolis is

a registered trademark of Amgen Inc. **Date of PI preparation:** November 2019 (Ref: UKIE-P-CARF-1015-116497(10))

This medicinal product is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. **Adverse events should also be reported to Amgen Limited on +44 (0) 1223 436441**