VELCADE® 3.5 mg POWDER FOR SOLUTION FOR INJECTION PRESCRIBING INFORMATION

ACTIVE INGREDIENT: Bortezomib

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATIONS: Adults only. Monotherapy or with pegylated liposomal doxorubicin or dexamethasone: progressive multiple myeloma in patients who have had at least 1 prior therapy and already undergone/are not suitable for haematopoietic stem cell transplant. With melphalan & prednisone: for previously untreated multiple myeloma in patients not eligible for high-dose chemotherapy with haematopoietic stem cell transplant. With dexamethasone, or with dexamethasone and thalidomide: for induction treatment of previously untreated multiple myeloma in patients eligible for high-dose chemotherapy with haematopoietic stem cell transplant. With rituximab, cyclophosphamide, doxorubicin and prednisone: for previously untreated mantle cell lymphoma (MCL) in patients unsuitable for haematopoietic stem cell transplantation.

DOSAGE & ADMINISTRATION: Adults and Elderly: Administer as 3-5 second IV bolus or SC in thighs/abdomen. At least 72 hours between consecutive doses. Recommended dose 1.3mg/m^2 body surface area. Posology modifications required for VELCADE-related toxicity, refer to SmPC.

Treatment of progressive multiple myeloma (after at least 1 prior therapy)

VELCADE treatment cycle: twice weekly for 2 weeks in 21-days treatment cycle. Two cycles of VELCADE recommended following confirmation of complete response. Responding patients without complete remission should receive total of 8 cycles. ***Monotherapy:*** as above. ***Combination with pegylated liposomal doxorubicin:*** 30 mg/m² pegylated liposomal doxorubicin (1h IV infusion) on day 4 of VELCADE treatment cycle. ***Combination with dexamethasone:*** 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 of VELCADE treatment cycle.

Previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplant

Combination with oral melphalan (9mg/m^2) and prednisone (60mg/m^2): 9 x 6-weeks treatment cycles.

Previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplant (induction therapy)

Combination with oral dexamethasone (40mg): 4 x 21-days treatment cycles.

Combination with oral dexamethasone (40mg) and thalidomide (50mg): 4 x 28-days treatment cycles. At least partial responders: 2 additional cycles. For other medicinal products, see appropriate SmPCs.

Previously untreated mantle cell lymphoma not suitable for haematopoietic stem cell transplantation

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP): 6 - 8 x 21-days treatment cycles. (For other medicinal products, see appropriate SmPCs.)

Children: no recommendation on posology can be made; refer to SmPC for current available data. **Hepatic Impairment:** mild - no dose adjustment; moderate or severe - start on reduced dose of 0.7 mg/m^2 per injection for first cycle, then possible increase to 1.0 mg/m^2 or reduction to 0.5 mg/m^2 based on tolerability. **Renal Impairment:** See precautions.

CONTRAINDICATIONS: Hypersensitivity to active substance, boron or any excipients. Acute diffuse infiltrative pulmonary and pericardial disease.

SPECIAL WARNINGS & PRECAUTIONS: Do not administer intrathecally. Monitor complete blood counts; consider platelet transfusion. GI toxicity very common; monitor closely. In MCL, transient neutropenia reported between cycles; monitor for signs/symptoms of infection, treat promptly; consider prophylactic granulocyte colony stimulating factors if delayed cycles. Herpes zoster virus reactivation: **anti-viral prophylaxis recommended**. Screen for Hepatitis B Virus reactivation/infection when rituximab combination; consider antiviral prophylaxis (see SmPC for rituximab). Very rarely John Cunningham virus infection resulting in Progressive Multifocal Leukoencephalopathy (PML) and death; monitor regularly for PML symptoms, discontinue if diagnosed. Peripheral neuropathy common; requires careful monitoring, neurological evaluation and possible dose/schedule modification, or change to SC route. Special care if risk factors for seizures. Caution when history of syncope with medicinal products linked with hypotension, or dehydration due to recurrent diarrhoea/vomiting. Discontinue treatment if Posterior Reversible Encephalopathy Syndrome (PRES) occurs. Development/exacerbation of congestive heart failure/QT prolongation; monitor closely if cardiac risk factors. Renal impairment common; monitor closely. Rarely acute diffuse infiltrative pulmonary disease of unknown aetiology e.g. pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS); baseline chest radiograph recommended. If new/worsening pulmonary symptoms perform prompt diagnostic evaluation and treat appropriately; consider benefit/risk ratio before continuing. Immunocomplex-mediated reactions e.g. serum sickness, polyarthritis with rash, proliferative glomerulonephritis: discontinue if severe. Bortezomib exposure increased in moderate/severe hepatic impairment; reduce doses, closely monitor. Patients with high pre-treatment tumour burden at risk of tumour lysis syndrome; monitor closely. Concomitant CYP3A4-inhibitors: monitor closely. Caution with CYP3A4 or CYP2C19 substrates.

SIDE EFFECTS: ***Very common:*** thrombocytopenia, neutropenia, anaemia, decreased appetite, neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, nausea, vomiting, diarrhoea, constipation, fatigue, pyrexia, asthenia. *Multiple Myeloma:* musculoskeletal pain. *MCL:* pneumonia, febrile neutropenia, leukopenia, lymphopenia, stomatitis, hair disorder.
Common: herpes zoster (inc disseminated & ophthalmic), herpes simplex, fungal infection, hypokalaemia, hyponatraemia, blood glucose abnormal, sleep disorders & disturbances, motor neuropathy, loss of consciousness (inc syncope), dizziness, dysgeusia, vision abnormal, hypotension, orthostatic hypotension, hypertension, dyspnoea, upper/lower respiratory tract infection, cough, gastrointestinal haemorrhage (inc mucosal), dyspepsia, abdominal distension, oropharyngeal pain, abdominal pain (inc gastrointestinal and splenic pain), oral disorder, rash, pruritus, muscle spasms, pain in extremity, oedema (inc peripheral), chills, malaise, weight decreased.
Multiple Myeloma: pneumonia, leukopenia, lymphopenia, dehydration, hypocalcaemia, enzyme abnormality, mood disorders & disturbances, anxiety disorder, lethargy, headache, eye swelling, conjunctivitis, vertigo, epistaxis, stomatitis, flatulence, hepatic enzyme abnormality, erythema, dry skin, muscular weakness, renal impairment, pain.
MCL: sepsis (inc septic shock), Herpes virus infection, bacterial infections, hypersensitivity, diabetes mellitus, fluid retention, neuropathies, encephalopathy, peripheral sensorimotor neuropathy, autonomic neuropathy, dysacusis (inc tinnitus), cardiac fibrillation (inc atrial), arrhythmia, cardiac failure (inc left and right ventricular), myocardial ischaemia, ventricular dysfunction, hiccups, gastritis, oral ulceration, abdominal discomfort, dysphagia, gastrointestinal inflammation, hepatotoxicity (inc liver disorder), dermatitis, musculoskeletal pain, urinary tract infection, injection site reaction, hyperbilirubinaemia, protein analyses abnormal, weight increased.

Other side effects include: tumour lysis syndrome, pulmonary hypertension, pancytopenia, anaphylactic shock/reaction, hearing impaired (up to and inc deafness),

cardiovascular disorder (inc cardiogenic shock), pulmonary embolism, acute respiratory distress syndrome, colitis (inc clostridium difficile), hepatic failure.
Multiple Myeloma: cardiac failure, Posterior Reversible Encephalopathy Syndrome, acute diffuse infiltrative pulmonary disorders, autonomic neuropathy, sepsis, herpes virus infection, meningitis, meningoencephalitis herpetic, Epstein-Barr virus infection, neoplasm malignant, leukaemia plasmacytic, mycosis fungoides, neoplasm benign, lymphadenopathy, febrile neutropenia, thrombotic microangiopathy (including thrombocytopenic purpura), hypersensitivity, type III immune complex mediated reaction, Cushing's syndrome, mental disorder, suicidal ideation, psychotic disorder, haemorrhage intracranial, peripheral sensory motor neuropathy, encephalopathy, neurotoxicity, cerebral haemorrhage, seizure disorders, paralysis, coma, Guillain-Barré syndrome, demyelinating polyneuropathy, eye haemorrhage, optic neuropathy, different degrees of visual impairment, cardiac tamponade, cardio-pulmonary arrest, cardiac fibrillation, arrhythmia, tachycardia, angina pectoris, pericarditis, cardiomyopathy, ventricular dysfunction, atrial flutter, myocardial infarction, atrioventricular block, torsade de pointes, angina unstable, cardiac valve disorders, sinus arrest, cerebrovascular accident, deep vein thrombosis, thrombophlebitis, phlebitis, vasculitis, peripheral embolism, pulmonary alveolar haemorrhage, bronchospasm, wheezing, respiratory failure, apnoea, haemoptysis, respiratory alkalosis, throat tightness, pancreatitis, haematemesis, gastro-intestinal obstruction, enteritis, megacolon, peritonitis, gastrointestinal ulceration & perforation, hepatotoxicity, hepatitis, cholestatis, hepatic haemorrhage, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, purpura, erythema multiforme, myopathies, rhabdomyolysis, renal failure, urinary retention, oliguria, death, multi-organ failure, ECG abnormality. *MCL:* hepatitis B infection, bronchopneumonia, autonomic nervous system imbalance, vertigo, pneumonitis, pulmonary oedema (inc acute). **Refer to SmPC for other side effects.**

LEGAL CATEGORY: Prescription Only Medicine

PRESENTATION, PACK SIZE, MARKETING AUTHORISATION NUMBER:

PRESENTATION	PACK SIZE	MARKETING AUTHORISATION NUMBER
3.5 mg vial	1 vial	EU/1/04/274/001

MARKETING AUTHORISATION HOLDER: JANSSEN-CILAG INTERNATIONAL NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

FURTHER INFORMATION IS AVAILABLE FROM: Janssen Sciences Ireland UC, Barnahely, Ringaskiddy, IRL - Co. Cork, P43 FA46.

Prescribing information last revised: February 2021

Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse events via: HPRA Pharmacovigilance, Earlsfort Terrace, Website: www.hpra.ie Adverse events should also be reported, Janssen Sciences Ireland UC, on 1800 709 122 or at dsafety@its.jnj.com