Important information regarding

RECONSTITUTION, DOSING AND ADMINISTRATION

of VELCADE® (bortezomib) 3.5 mg vial for Subcutaneous (SC) and Intravenous (IV) use

VELCADE®
(bortezomib)

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(bortezomib)

CORRECT RECONSTITUTION FOR SC AND IV ADMINISTRATION

VELCADE® (bortezomib) 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration, VELCADE® 1 mg powder for solution for injection is available for intravenous administration only.

Subcutaneous or Intravenous use only.
Do not give by other routes.
Intrathecal administration has resulted in death.

VELCADE® must be reconstituted by a Health Care Professional. Aseptic technique must be strictly observed throughout the handling of VELCADE® since no preservative is present.

Avoiding the potential risk of administration errors

In order to avoid dosing errors, caution is required when preparing VELCADE® as the volume required for reconstitution for the SC route is lower (1.4 ml) than that used for IV use (3.5 ml) giving a higher concentration of diluted drug (details are shown in tables 1 and 2).

As the drug concentration after reconstitution differs between the SC and IV preparations, special care is required when calculating the volume of reconstituted drug, which will be delivered to the patient according to the prescribed dose. Please see pages 8-10 for examples of dosing for the different routes.

VELCADE®
(bortezomib)

SUBCUTANEOUS ROUTE OF ADMINISTRATION

Preparation of the 3.5 mg vial

Each 3.5 mg vial of VELCADE® must be reconstituted with 1.4 ml sterile sodium chloride 9 mg/ml (0.9 %) solution for injection – dissolution of the lyophilised powder is completed in less than 2 minutes.

Reconstitute the powder with 1.4 ml sodium chloride: inject the sodium chloride solution into the vial containing the lyophilised VELCADE®.

Table 1: Reconstitution of 3.5 mg VELCADE® solution for SC injection

Route of administration	Pack size	Reconstitution volume	Final concentration
Subcutaneous use only	3.5 mg	1.4 ml	2.5 mg/ml

Reconstitution volume is less than that used for IV giving a more concentrated drug solution for injection

The reconstituted solution should be clear and colourless.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

The final concentration is 2.5 mg/ml.

PLEASE NOTE: The final drug concentration, when reconstituted for SC administration (2.5 mg/ml), is 2.5 times higher than that for the IV route (1 mg/ml) and therefore the volume required is lower when the SC route of administration is used.

Once dissolved, withdraw the appropriate amount of the reconstituted drug solution: according to calculated dose based upon the patient´s Body Surface Area (BSA).

To avoid administration errors, syringes for SC and IV use should be labelled differently.

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INTRAVENOUS ROUTE OF ADMINISTRATION

Preparation of the 3.5 mg vial

Each 3.5 mg vial of VELCADE® must be reconstituted with 3.5 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection – Dissolution of the lyophilised powder is completed in less than 2 minutes.

Reconstitute the powder with 3.5 ml sodium chloride: inject the sodium chloride solution into the vial containing the lyophilised VELCADE®.

Table 2: Reconstitution of 3.5 mg VELCADE® solution for IV injection

Route of administration	Pack size	Reconstitution volume	Final concentration
Intravenous use	3.5 mg	3.5 ml	1.0 mg/ml

Reconstitution volume is more than that used for SC giving a less concentrated drug solution for injection

The reconstituted solution should be clear and colourless.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

The final concentration is 1.0 mg/ml.

Once dissolved, withdraw the appropriate amount of the reconstituted drug solution: according to calculated dose based upon the patient´s Body Surface Area (BSA).

To avoid administration errors, syringes for SC and IV use should be labelled differently.

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DOSING EXAMPLES FOR SC & IV ADMINISTRATION

Calculate the BSA using the slide rule. Additional examples are provided with the dosing slide rule.

BSA: 1.7 m^2, Dose: 1.3 mg/m^2

Intravenous Sample patient (1.7 m^2)	**Subcutaneous** Sample patient (1.7 m^2)
Vial size: 3.5 mg lyophilisate	**Vial size:** 3.5 mg lyophilisate
Diluent volume: 3.5 ml saline	**Diluent volume:** 1.4 ml saline
Final concentration **1 mg/ml**	**Final concentration** **2.5 mg/ml**
Dose: 1.3 mg/m^2	**Dose:** 1.3 mg/m^2
Total dose for patient: **2.21 mg**	**Total dose for patient:** **2.21 mg**
Total volume* applied to the patient: 2.2 ml	**Total volume* applied to the patient:** **0.9 ml**
Injected IV (3-5 seconds push)	**Injected SC**

*Total volume rounded

NOTE: If the calculated IV volume is used with the SC concentration, the patient will be overdosed.

If the calculated SC volume is used with the IV concentration the patient will be underdosed.

BSA: 1.95 m², Dose: 1.3 mg/m²

Intravenous Sample patient (1.95 m²)	Subcutaneous Sample patient (1.95 m²)
Vial size: 3.5 mg lyophilisate	**Vial size:** 3.5 mg lyophilisate
Diluent volume: 3.5 ml saline	**Diluent volume:** 1.4 ml saline
Final concentration 1 mg/ml	**Final concentration 2.5 mg/ml**
Dose: 1.3 mg/m² **Total dose for patient*:** **2.54 mg**	**Dose:** 1.3 mg/m² **Total dose for patient*:** **2.54 mg**
Total volume* applied to the patient: 2.5 ml	**Total volume* applied to the patient: 1 ml**
Injected IV (3-5 seconds push)	**Injected SC**

*Total volume rounded

NOTE: If the calculated IV volume is used with the SC concentration, the patient will be overdosed.

If the calculated SC volume is used with the IV concentration the patient will be underdosed.

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BSA: 1.6 m², Dose: 1.0 mg/m²

Intravenous Sample patient (1.6 m²)	Subcutaneous Sample patient (1.6 m²)
Vial size: 3.5 mg lyophilisate	**Vial size:** 3.5 mg lyophilisate
Diluent volume: 3.5 ml saline	**Diluent volume:** 1.4 ml saline
Final concentration **1 mg/ml**	**Final concentration** **2.5 mg/ml**
Dose: 1.0 mg/m²	**Dose:** 1.0 mg/m²
Total dose for patient: **1.6 mg**	**Total dose for patient:** **1.6 mg**
Total volume* **applied to the patient:** **1.6 ml**	**Total volume*** **applied to the patient:** **0.64 ml**
Injected IV (3-5 seconds push)	**Injected SC**

*Total volume rounded

NOTE: If the calculated IV volume is used with the SC concentration, the patient will be overdosed.

If the calculated SC volume is used with the IV concentration the patient will be underdosed.

GENERAL INFORMATION

General Precautions

VELCADE® is a cytotoxic agent. Therefore, caution should be applied when handling and preparing VELCADE®. The use of gloves and other protective clothing to prevent skin contact is recommended.

Please report any adverse event experienced with the administration of VELCADE® immediately.

Subcutaneous or Intravenous use only. Do not give by other routes. Intrathecal administration has resulted in death.

Shelf life

3 Years.

Reconstituted solution

VELCADE® is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The reconstituted product is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and / or syringe, with a total storage time for the reconstituted medicinal product not exceeding 8 hours prior to administration. It is not necessary to protect the reconstituted medicinal product from light.

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CORRECT ADMINISTRATION FOR SC & IV VELCADE®

How to administer VELCADE® SC?

Confirm the dose in the syringe prior to use (check that the syringe is marked as SC administration).

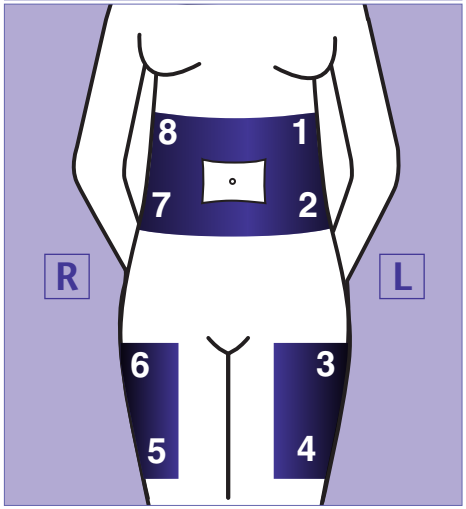
Inject the solution subcutaneously, at a 45-90 °angle.

The reconstituted solution should be administered subcutaneously in the thighs or abdomen and injection sites should be rotated for successive injections.

- **Injections at the same site should be avoided**
  - Alternate between
    - right and left abdomen (upper or lower quadrant)
    - right and left thigh (proximal and distal sites)

Remind the patient to take the antiviral prophylaxis.

Figure1. Injection site rotation



How to administer VELCADE® IV?

Confirm the dose in the syringe prior to use (check that the syringe is marked for IV administration).

Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein. The use of IV hydration and an antiemetic medication as concomitant therapy prior to administration of IV VELCADE® is recommended. Remind the patient to take the antiviral prophylaxis.

Flush the peripheral or intravenous catheter with sterile 9 mg/ml (0.9 %) sodium chloride solution.

Please report any adverse event experienced with the administration of VELCADE® immediately.

VELCADE®▼ 3.5 mg POWDER FOR SOLUTION FOR INJECTION
PRESCRIBING INFORMATION

ACTIVE INGREDIENT: Bortezomib

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

INDICATION(S): Monotherapy of progressive multiple myeloma in adult patients who have had at least 1 prior therapy and already undergone or are not suitable for bone marrow transplantation. With melphalan & prednisolone for treating previously untreated multiple myeloma in adult patients who are not eligible for high-dose chemotherapy with bone marrow transplant.

DOSAGE & ADMINISTRATION: Adults and Elderly: VELCADE 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration. VELCADE should not be given by other routes. Intrathecal administration has resulted in death.
Intravenous: Reconstituted solution contains 1mg/ml and administered as 3-5 second IV bolus.
Subcutaneous: Reconstituted solution contains 2.5mg/ml and is administered SC through thighs or abdomen. Injection sites should be rotated for successive injections.
At least 72 hours should elapse between consecutive doses. Recommended starting dose 1.3mg/m^2 body surface area.
Monotherapy: twice weekly for two weeks followed by a 10-day rest period.
When administered as a single agent, treatment should be withheld in the presence of any Grade 3 non-haematological or Grade 4 haematological toxicity, excluding neuropathy. Treatment may be restarted at an approximate 25% dose reduction (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2) following resolution of toxicity.
The dose should be reduced to 1 mg/m^2 or change treatment schedule to 1.3.mg/m^2 once per week in the presence of Grade 1 with pain or Grade 2 moderate symptoms; limiting instrumental Activities of Daily Living (ADL) neuropathy.
In the presence of Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL) neuropathy, treatment should be withheld until symptoms of toxicity have resolved. Reinitiate treatment at a dose of 0.7 mg/ m^2 once per week.
If Grade 4 (life-threatening consequences; urgent intervention indicated) and /or severe autonomic neuropathy occur, discontinue treatment permanently.
Combination therapy: VELCADE is administered in combination with oral melphalan (9mg/m^2) and prednisolone (60mg/m^2) for nine treatment cycles. A 6-week period is considered a treatment cycle. Refer to SmPC for dose management.
When administered in combination with melphalan and prednisolone, treatment should be withheld if either the platelet counts ≤30 ˙ 10^9/l or ANC ≤0.75 x 10^9/l on a VELCADE dosing day (other than Day 1). Consideration should be given to reducing subsequent doses by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2) if several doses (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration) are withheld in any one cycle of treatment.
Treatment should be withheld until any ≥Grade 3 non-haematological toxicities have returned to Grade 1 or baseline. Retreatment should be initiated with one dose level reduction. During combination therapy the dose should be held and/or modified in the presence of VELCADE-related neuropathic pain and/or peripheral neuropathy in the same way as monotherapy.
Children: Not applicable. **Hepatic Impairment:** mild - no dose adjustment; moderate or severe - start on reduced dose of 0.7 mg/m^2 per injection for first cycle, and 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 bortezomib, boron or any of the excipients.
Acute diffuse infiltrative pulmonary and pericardial disease.

SPECIAL WARNINGS & PRECAUTIONS: Do not administer intrathecally. Monitor complete blood counts including platelets. Gastrointestinal toxicity is very common, monitor closely. Herpes zoster virus reactivation: anti-viral prophylaxis should be considered. Peripheral neuropathy is common and requires careful monitoring. Patients should undergo neurological evaluation and possible dose or schedule modification, or a change to subcutaneous administration. Special care of patients with risk factors for seizures. Caution is advised when history of syncope on receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Discontinue treatment if Posterior Reversible Encephalopathy Syndrome (PRES) occurs. Development or exacerbation of congestive heart failure, QT prolongation. Monitor closely patients with cardiac risk factors and those with renal impairment. Rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology e.g. pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS). A baseline pretreatment chest radiograph is recommended. In event of new or worsening pulmonary symptoms perform prompt diagnostic evaluation and treat appropriately. Consider benefit/risk ratio before continuing VELCADE therapy. Immunocomplex-mediated reactions e.g. serum sickness, polyarthritis with rash, proliferative glomerulonephritis: discontinue if severe. Bortezomib exposure is increased in moderate/severe hepatic impairment: treat at reduced doses and closely monitor for toxicities. Patients with high pre-treatment tumour burden are at risk of tumour lysis syndrome: monitor closely. Monitor patients closely when given concomitant CYP3A4-inhibitors. Exercise caution when combined with CYP3A4 or CYP2C19 substrates.

SIDE EFFECTS: ***Very common:*** thrombocytopenia, neutropenia, anaemia, leukopenia, appetite decreased, peripheral neuropathy, peripheral sensory neuropathy, dysaesthesia, neuralgia, headache, vomiting, diarrhoea, nausea, constipation, abdominal pain (inc gastrointestinal pain), rash, musculoskeletal pain, fatigue, pyrexia, asthenia.

Common: herpes zoster (inc disseminated & ophthalmic) - **consider anti-viral prophylaxis**, pneumonia, infection, herpes simplex, fungal infection, lymphopenia, electrolyte imbalance, dehydration, enzyme abnormality, hyperuricaemia, mood altered, anxiety disorder, sleep disorder, peripheral motor neuropathy, loss of consciousness (inc syncope), dizziness, dysgeusia, lethargy, eye swelling, vision abnormal, conjunctivitis, dry eye, vertigo, cardiac failure, tachycardia, hypotension, orthostatic hypotension, hypertension, dyspnoea, epistaxis, upper/lower respiratory tract infection, cough, gastrointestinal haemorrhage (inc mucosal), dyspepsia, stomatitis, abdominal distension, oropharyngeal pain, abdominal discomfort, oral disorder, flatulence, hepatic enzyme abnormality, urticaria, pruritus, erythema, dermatitis, dry skin, muscle spasms, pain in extremity, muscular weakness, renal impairment, renal failure chronic, oedema (inc peripheral), chills, pain, injection site reaction, malaise, weight decreased.

Other side effects include: sepsis, herpes virus infection, meningitis (inc bacterial), Epstein-Barr virus infection, neoplasm malignant, leukaemia plasmacytic, mycosis fungoides, neoplasm benign, lymphadenopathy, pancytopenia, febrile neutropenia, thrombocytopenic purpura, hypersensitivity, immunocomplex mediated hypersensitivity, potentially hypersensitivity, anaphylactic shock, Type III immune complex mediated reaction, Cushing's syndrome, tumour lysis syndrome, hypoglycaemia, delirium, hallucination, restlessness, mental disorder, suicidal ideation, psychotic disorder, haemorrhage intracranial, peripheral sensory motor neuropathy, encephalopathy, neurotoxicity, restless leg syndrome, cerebral haemorrhage, convulsion, paralysis, eye haemorrhage, optic neuropathy, different degrees of visual impairment (up to blindness), hearing impaired (up to and inc deafness), dysacusis, cardio-pulmonary arrest, cardiac fibrillation (inc atrial) arrhythmia, angina pectoris, pericarditis, cardiomyopathy, ventricular dysfunction, atrial flutter, myocardial infarction, atrioventricular block, cardiovascular disorder (inc cardiogenic shock), torsade de pointes, angina unstable, left ventricular failure, sinus arrest, thrombophlebitis (inc superficial), phlebitis, vasculitis, peripheral embolism, pulmonary embolism, bronchospasm, pulmonary hypertension, pulmonary fibrosis, wheezing, respiratory failure, acute respiratory distress syndrome, apnoea, haemoptysis, respiratory alkalosis, throat tightness, pancreatitis (inc chronic), haematemesis, ileus, enteritis, pancreatitis acute, ileus paralytic, peritonitis, hepatotoxicity (inc liver disorder), hepatitis, cholestatis, hepatic failure, hepatic haemorrhage, acute febrile neutrophilic dermatosis, toxic skin eruption, petechiae, ecchymosis, purpura, erythema multiforme, photosensitivity reaction, muscle stiffness, joint stiffness/swelling, myopathy, rhabdomyolysis, renal failure acute, oliguria, death (inc sudden), face oedema, blood bicarbonate decreased, protein urine present.
Refer to SmPC for other side effects.

PREGNANCY: Not fully established. Male and female patients of childbearing potential must use effective contraceptive measures during treatment and for 3 months following.

LACTATION: Not recommended.

INTERACTIONS: Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). Concomitant use of bortezomib with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort), is not recommended. *In vitro* studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. No clinically relevant interaction between melphalan-prednisolone and VELCADE (IV). In clinical trials, hypo/hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics.

LEGAL CATEGORY: POM

PRESENTATIONS, PACK SIZES, PRODUCT LICENCE NUMBERS: 1 vial per pack. EU/1/04/274/001.

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

FURTHER INFORMATION IS AVAILABLE FROM:
Prescribing information last revised: September 2012

ANY SUSPECTED ADVERSE DRUG REACTIONS CAN BE REPORTED TO:
Medicines Authority Post-Licensing Directorate, 203 Level 3, Rue D'Argens, Gzira GZR1368, Malta, or at http://medicinesauthority.gov.mt/pub/adr.doc

FOR MORE INFORMATION CONTACT:
A.M. Mangion Ltd, Mangion Buildings, New Street in Valletta Road, Luqa LQA 6000, Malta Tel. 00 356 2397 6000.

Please refer to Summary of Product Characteristics (SmPC) for further instructions

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