PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VELBOR IV, lyophilised powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3,5 mg bortezomib (mannitol boronic ester). VELBOR IV is for both intravenous and subcutaneous use.

Intravenous injection: After reconstitution, each 1 mL of solution contains 1 mg bortezomib.

Subcutaneous injection: After reconstitution each 1 mL of solution contains 2,5 mg bortezomib.

VELBOR IV contains sugar (35 mg mannitol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for solution for injection. A white to off-white lyophilised mass.

After reconstitution with 0,9 % sodium chloride solution for injection:

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VELBOR IV is indicated as:

- primary treatment of multiple myeloma in combination with melphalan and prednisone
- monotherapy for the treatment of patients with multiple myeloma who have received at least one prior therapy and who have progressive disease
- treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.

4.2 Posology and method of administration

Posology

VELBOR IV lyophilised powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg/mL (as a 3 – 5 second bolus injection)

  or

- subcutaneous administration at a concentration of 2,5 mg/mL.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered (see section 6.6).

VELBOR IV should not be given by other routes. Intrathecal administration has resulted in death.

Refer to Reconstitution Instructions in section 6.6.

MONOTHERAPY:

Recommended dosage:

The recommended starting dose of VELBOR IV is 1,3 mg/m^2 body surface area twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12 - 21). This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELBOR IV.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of VELBOR IV beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VELBOR IV therapy.

There is limited data concerning re-treatment with VELBOR IV.

Recommended dosage adjustments during treatment and re-initiation of treatment:

VELBOR IV treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see section 4.4). Once the

symptoms of the toxicity have resolved, VELBOR IV treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2; 1,0 mg/m^2 reduced to 0,7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELBOR IV must be considered.

Patients who experience VELBOR IV related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1. Patients with pre-existing severe neuropathy may be treated with VELBOR IV only after careful risk/benefit assessment.

Table 1: Recommended dose modifications for VELBOR IV related Neuropathic Pain and/or Peripheral Sensory Neuropathy:

Severity of peripheral neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not activities of daily living)	Reduce to 1,0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELBOR IV treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELBOR IV treatment and reduce dose to 0,7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELBOR IV

COMBINATION THERAPY:

Recommended dosage

VELBOR IV (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2.

In Cycles 1 – 4, VELBOR IV is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 – 9, VELBOR IV is administered once weekly (days 1, 8, 22 and 29).

Table 2: Recommended dosage regimen for VELBOR IV when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma

Twice weekly VELBOR IV (Cycles 1 – 4)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
V (1,3 mg/m^2)	Day 1 & 4	Day 8 & 11	rest period	Day 22 & 25	Day 29 & 32	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1, 2, 3 & 4	---	rest period	---	---	rest period
Once weekly VELBOR IV (Cycles 5 – 9)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
V (1,3 mg/m^2)	Day 1	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1, 2, 3 & 4	---	rest period	---	---	rest period

V = VELBOR IV, m = melphalan, p = prednisone

Dose management guidelines for combination therapy:

Dose modification and re-initiation of therapy when VELBOR IV is administered in combination with melphalan and prednisone:

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/L and the ANC should be ≥ 1,0 x 10^9/L
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Table 3: Dose modifications during subsequent cycles:

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle
If platelet count ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a VELBOR IV dosing day (other than day 1)	VELBOR IV dose should be withheld
If several VELBOR IV doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VELBOR IV dose should be reduced 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)
Grade ≥ 3 non-haematological toxicities	VELBOR IV therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELBOR IV may then be re-initiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2). For VELBOR IV-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELBOR IV as outlined in Table 1.

For additional information concerning melphalan and prednisone, see the respective professional information inserts.

Special populations

Paediatric patients:

The safety and efficacy of VELBOR IV has not been established in children and adolescents. Therefore, it should not be used in the paediatric age group until further data becomes available.

Elderly patients:

There is no evidence to suggest that dose adjustments are necessary in the elderly (see section 4.8).

Patients with Renal Impairment:

The pharmacokinetics of VELBOR IV are not influenced by the degree of renal impairment. Therefore, dosing adjustment of VELBOR IV are not necessary for patients with renal insufficiency. Since dialysis may reduce VELBOR IV concentrations. VELBOR IV should be administered after the dialysis procedure (see section 5.2).

Patients with Hepatic Impairment:

Patient with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELBOR IV dose. Patients with moderate or severe hepatic impairment should be started on VELBOR IV at a reduced dose of 0,7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see Table 4).

Table 4: Recommended starting dose modification for VELBOR IV in patients with Hepatic Impairment:

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) levels**	**Modification of starting dose**
Mild	≤ 1,0 x ULN	> ULN	None
	> 1,0 x - 1,5 x ULN	Any	
Moderate	> 1,5 x - 3 x ULN	Any	Reduce VELBOR IV to 0,7 mg/m^2 in the first cycle. Consider dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations:

SGOT = serum glutamic oxaloacetic transaminase:

AST = aspartame aminotransferase,

ULN = upper limit of the normal range.

*Based on NCl Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Method of administration

Administration precautions

There have been fatal cases of inadvertent intrathecal administration of VELBOR IV.

DO NOT ADMINISTER VELBOR IV INTRATHECALLY.

Intravenous injection:

The reconstituted solution is administered as a 3 – 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of VELBOR IV.

Subcutaneous injection:

The reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red or hard.

If local injection site reactions occur following VELBOR IV injection subcutaneously, a less concentrated VELBOR IV solution (1 mg/mL instead of 2,5 mg/mL) may be administered subcutaneously or changed to an IV injection.

4.3 Contraindications

- Hypersensitivity to bortezomib, boron or to any of the ingredients of VELBOR IV
- Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

When VELBOR IV is given in combination with other medicines, the Professional Information of these other medicines must be consulted prior to initiation of treatment with VELBOR IV.

Treatment must be initiated and administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicines.

DO NOT ADMINISTER VELBOR IV INTRATHECALLY.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. VELBOR IV lyophilised powder for solution for injection is for intravenous and subcutaneous use only and should not be administered intrathecally.

Pulmonary Disorders:

There have been reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELBOR IV. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed, and patients treated appropriately.

Herpes zoster virus reactivation:

Healthcare providers should consider using antiviral prophylaxis in patients being treated with VELBOR IV. Studies have shown that in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation is common in patients treated with VELBOR IV/melphalan/prednisone (VMP), and that after administration of an antiviral prophylaxis to patients

receiving VMP, the incidence of herpes zoster is reduced compared to those not administered antiviral prophylaxis.

Patients with mantle cell lymphoma:

The safety profile of VELBOR IV in patients with mantle cell lymphoma is similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations are that thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia occur more frequently in patients with multiple myeloma; whereas peripheral neuropathy, rash and pruritus is higher among patients with mantle cell lymphoma.

Overall, the safety profile of patients treated with VELBOR IV in monotherapy is similar to that observed in patients treated with VELBOR IV in combination with melphalan and prednisone.

Laboratory tests:

Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with VELBOR IV.

Gastrointestinal toxicity:

Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with VELBOR IV treatment (see section 4.8). Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of antiemetics and antidiarrhoeal medicines. Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been reported, therefore patients who experience constipation should be closely monitored.

Haematological toxicity:

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia and neutropenia). However, febrile neutropenia is an uncommon side effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment

cycles. Platelets are lowest at Day 11 of each cycle of VELBOR IV treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet decreases and recovery remain consistent over the 8 cycles of twice weekly dosing and there is no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured is approximately 40 % of baseline. Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count. Platelet counts should be monitored prior to each dose of VELBOR IV. Therapy should be held when the platelet count is < 25 000/µl and re-initiated at a reduced dose after resolution (see section 4.8). Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Peripheral Neuropathy:

VELBOR IV treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported.

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with VELBOR IV. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of VELBOR IV to be modified (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on

autonomic neuropathy and its contribution to these side effects is limited. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Seizures:

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension:

VELBOR IV treatment is commonly associated with orthostatic/postural hypotension, for which most patients require treatment. Patients with orthostatic hypotension are known to experience syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to VELBOR IV or VELBOR IV may aggravate an underlying condition such as diabetic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension is symptomatic and may include adjustment of antihypertensive medicines, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Cardiac disorders:

Development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported. Patients with risk factors for, or existing heart disease should be closely monitored. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. There have been isolated cases of QT-interval prolongation, although causality has not been established.

Patients using angiotensin inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during VELBOR IV treatment.

Renal events:

Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely.

Hepatic events:

Cases of acute liver failure have been reported. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinemia and hepatitis. Such changes may be reversible upon discontinuation of VELBOR IV. There is limited re-challenge information in these patients.

Hepatic Impairment:

Bortezomib is metabolised by liver enzymes. VELBOR IV exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with VELBOR IV at reduced starting doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatitis B virus (HBV) reactivation and infection:

When rituximab is used in combination with VELBOR IV, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with VELBOR IV. Antiviral prophylaxis should be considered.

Tumour lysis syndrome:

Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrhythmias and syncope. These patients should be monitored closely, and appropriate precautions taken.

Amyloidosis:

The impact of proteasome inhibition by VELBOR IV on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

Potentially immunocomplex-mediated reactions:

Potentially immunocomplex-mediated reactions, such as serum-sickness–type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. VELBOR IV should be discontinued if severe reactions occur.

Posterior Reversible Encephalopathy Syndrome (PRES):

There have been reports of PRES in patients receiving VELBOR IV. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELBOR IV. The safety of reinitiating VELBOR IV therapy in patients previously experiencing PRES is not known.

Progressive Multifocal Leukoencephalopathy (PML):

Cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELBOR IV. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELBOR IV. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue VELBOR IV if PML is diagnosed.

Porphyria:

Bortezomib is possibly porphyrinogenic and should be used only when no safer alternative is available, and precautions should be considered in vulnerable patients.

Concomitant medicines

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see section 4.5).

Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics (see section 4.5).

Immune system:

A patient's immune system may be suppressed whilst on VELBOR IV therapy, with antibody response to vaccines decreased. Concurrent use with a live virus vaccine is not recommended, since there is a possibility of generalised infection.

4.5 Interaction with other medicines and other forms of interaction

In-vitro studies indicate bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7 %) of CYP2D6 to the metabolism of bortezomib the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of VELBOR IV.

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35 % based on data from 12 patients. Therefore, patients should be closely monitored when given VELBOR IV in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

An interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of bortezomib, showed no significant effect on the pharmacokinetics of bortezomib. Rifampicin, a potent CYP3A4 inducer, reduces the mean AUC of bortezomib by approximately 45 %. The concomitant use of VELBOR IV with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin,

phenobarbital and St. John's Wort. Dexamethasone, a weaker CYP3A4 inducer, shows no significant effect on the pharmacokinetics of bortezomib.

Concomitant exposure of VELBOR IV and narcotics may increase the incidence of constipation, nausea and vomiting.

An interaction study assessing the effect of melphalan-prednisone on bortezomib showed a 17 % increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving VELBOR IV treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication. Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Women of childbearing potential / Contraception in males and females

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 3 months following VELBOR IV therapy.

Pregnancy

No clinical data are available for bortezomib with regard to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

If VELBOR IV is used during pregnancy, or if the patient becomes pregnant while receiving VELBOR IV, the patient needs to be informed of potential for hazards to the foetus.

Breastfeeding

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from bortezomib, women should not breastfeed their infants while receiving VELBOR IV.

Fertility

Fertility studies were not conducted with VELBOR IV.

4.7 Effects on ability to drive and use machines:

VELBOR IV may have a moderate influence on the ability to drive and use machines. VELBOR IV may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when operating machinery, or when driving.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions less frequently reported during treatment with VELBOR IV include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and autonomic neuropathy.

The most frequently reported adverse reactions during treatment with VELBOR IV are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated list of adverse effects

Adverse reactions in patients with multiple myeloma treated with VELBOR IV as single agent or in combination, including post-marketing adverse reactions:

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Herpes zoster (including disseminated & ophthalmic), pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex, fungal infection
	Less frequent	Sepsis, bacteraemia (including staphylococcal), pneumonia pneumococcal, bronchopneumonia, upper and lower respiratory tract infection, catheter related infection, pleural infection, haemophilus infection, cytomegalovirus infection, influenza, infectious mononucleosis, varicella, urinary tract infection, gastroenteritis, candida infection, fungal infection, post herpetic neuralgia, oral candidiasis, blepharitis, infection, skin infection, ear infection, tooth infection, hordeolum, cellulitis, device related infection, herpes virus infection, Epstein-Bar virus infection, meningitis (including bacterial) genital herpes, tonsillitis, mastoiditis, post-viral fatigue syndrome
	Frequency unknown	Herpes meningoencephalitis, septic shock, progressive multifocal leukoencephalopathy
Neoplasms benign and malignant (including cysts and polyps)	Less frequent	Neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign

Blood and lymphatic system disorders	Frequent Less frequent	Thrombocytopenia, neutropenia, anaemia, leucopenia, lymphopenia Pancytopenia, febrile neutropenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy, coagulopathy, leucocytosis, disseminated intravascular coagulation, thrombocytosis, hyperviscosity syndrome, platelet disorder NOS, blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity, immunocomplex mediated hypersensitivity, potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash, proliferative glomerulonephritis, anaphylactic shock, angioedema, amyloidosis Angioedema
Endocrine disorders	Less frequent	Inappropriate antidiuretic hormone (ADH) secretion, Cushing's syndrome, hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders	Frequent Less frequent	Appetite decreased, dehydration, hypokalaemia, hyperglycaemia Hyperkalaemia, cachexia, hypercalcaemia, hypocalcaemia, hypernatremia, hyponatraemia, hypoglycaemia, hyperuricaemia, vitamin B12 and vitamin B complex deficiency, appetite increased, hypomagnesaemia, hypophosphatemia, tumour lysis syndrome, uric acid abnormal, diabetes mellitus, fluid retention, hypermagnesemia, acidosis, electrolyte imbalance, fluid overload, hyperchloremia, hypovolemia,

		hypochloraemia metabolic disorder, gout, increased appetite, alcohol intolerance
Psychiatric disorders	Frequent Less frequent	Confusion, depression, insomnia, anxiety Agitation, delirium, hallucinations, restlessness, mood swings, mental status changes, sleep disorder, irritability, abnormal dreams, suicidal ideation, adjustment disorder, psychotic disorder
Nervous system disorders	Frequent Less frequent <

Eye disorders	Frequent Less frequent Frequency unknown	Vision blurred, eye pain Eye haemorrhage, vision abnormal, keratitis sicca, conjunctivitis, eye discharge, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling, diplopia, dry eye Ophthalmic herpes, optic neuropathy, blindness
Ear and labyrinth disorders	Frequent Less frequent Frequency unknown	Vertigo Deafness, tinnitus, hypoacusis, hearing impaired Deafness bilateral
Cardiac disorders	Less frequent Frequency unknown	Cardiac arrest, cardiogenic shock, myocardial infarction, angina pectoris, angina unstable, development or exacerbation of congestive heart failure, cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, atrioventricular block complete, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations, new onset of decreased left ventricular ejection fraction, pericarditis Cardiac tamponade
Vascular disorders	Frequent Less frequent	Hypotension, orthostatic and postural hypotension, hypertension, phlebitis, haematoma Cerebral haemorrhage, vasculitis**,** cerebrovascular accident, pulmonary hypertension, petechiae, ecchymosis, purpura, vein discolouration, vein distended, wound haemorrhage, flushing, hot flushes, deep vein

		thrombosis, circulatory collapse including hypovolemic shock, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, venous insufficiency
	Frequency unknown	Cerebrovascular accident
Respiratory, thoracic and mediastinal disorde	Frequent	Dyspnoea, dyspnoea exertional, epistaxis, cough, rhinorrhoea, upper/lower respiratory tract infection
	Less frequent	Respiratory arrest, hypoxia, pulmonary congestion, pulmonary embolism, pulmonary oedema, pleural effusion, asthma, respiratory alkalosis, tachypnoea, wheezing, nasal congestion, hoarseness, rhinitis, hyperventilation, orthopnoea, chest wall pain, sinus pain, throat tightness, productive cough, bronchospasm, chronic obstructive pulmonary disease, hypoxaemia, pleurisy, apnoea, pneumothorax, atelectasis, haemoptysis, hyperventilation, orthopnoea, pneumonitis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial disorder, hypocapnia, interstitial lung disease, lung infiltration, throat tightness, dry throat, increased upper airway secretion, throat irritation, upper-airway cough syndrome
	Frequency unknown	Acute diffuse infiltrative pulmonary disease, pulmonary hypertension, pulmonary alveolar haemorrhage
Gastrointestinal disorders	Frequent	Vomiting, diarrhoea, nausea, constipation, abdominal pain, stomatitis, dyspepsia, loose stools, abdominal pain upper, flatulence, abdominal distension, hiccups, mouth ulceration, pharyngolaryngeal pain, dry mouth

	Less frequent Frequency unknown	Acute pancreatitis, ileus paralytic, antibiotic associated colitis, colitis, haematemesis, diarrhoea haemorrhagic, gastrointestinal haemorrhage, rectal haemorrhage, enteritis, dysphagia, abdominal discomfort, eructation, gastrointestinal motility disorder, oral pain, retching, change in bowel habit, spleen pain, oesophagitis, gastritis, gastro-oesophageal reflux disease, gastrointestinal pain, gingival bleeding, gingival pain, hiatus hernia, irritable bowel syndrome, oral mucosal petechiae, salivary hypersecretion, tongue coated, tongue discolouration, faecal impaction, lip swelling, gastrointestinal obstruction, irritable bowel syndrome, tongue oedema, ascites, cheilitis, faecal incontinence, anal sphincter, atony, faecaloma, gastrointestinal ulceration/perforation, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces Ischeamic colitis, intestinal obstruction
Hepato-biliary disorders	Frequent Less frequent	Hepatic enzyme abnormality Hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinemia, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, cholelithiasis
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash, periorbital oedema, urticaria, rash pruritic, pruritus, erythema, sweating increased, dry skin, eczema Vasculitic rash (including leukocytoclastic vasculitis), rash erythematous, photosensitivity reaction, contusion, generalised pruritus, macular rash, papular rash,

		psoriasis, generalised rash, eyelid oedema, face oedema, dermatitis, alopecia, nail disorder, skin discolouration, dermatitis atopic, hair texture abnormal, heat rash, night sweats, pressure sore, ichthyosis, skin nodule, erythema multiforme, toxic skin eruption, skin lesion, skin mass, hyperhidrosis, acne, blister, Lessner's lymphocytic infiltration, palmar-plantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, seborrhoea, cold sweat, erythrosis, skin ulcer
	Frequency unknown	Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute febrile neutrophilic dermatosis (Sweet's syndrome), decubitus ulcer
Musculoskeletal, connective tissue and bone disorders	Frequent	Myalgia, muscle weakness, musculoskeletal pain, pain in limb, muscle cramps, arthralgia, bone pain, back pain, peripheral swelling
	Less frequent	Muscle spasms, muscle twitching or sensation of heaviness, muscle stiffness, joint swelling, joint stiffness, buttock pain, swelling, pain in jaw, myopathies, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, bone disorder, musculoskeletal and connective tissue infections and inflammations, synovial cyst
Renal and urinary disorders	Frequent	Renal impairment, dysuria
	Less frequent	Renal failure acute, renal failure chronic, oliguria, renal colic, haematuria, proteinuria, urinary retention, urinary frequency, difficulty in micturition, loin pain, urinary

	Frequency unknown	incontinence, micturition urgency, azotaemia, bladder irritation Haemorrhagic cystitis
Reproductive system and breast disorders	Less frequent	Testicular pain, erectile dysfunction, vaginal haemorrhage, genital pain, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration, libido decreased
Congenital and familial/genetic disorders	Less frequent	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administrative site conditions	Frequent Less frequent	Fatigue, pyrexia, asthenia, weakness, lethargy, rigors, malaise, influenza like illness, oedema peripheral, chest pain, pain, oedema Fall, mucosal haemorrhage, mucosal inflammation, neuralgia, injection site phlebitis, extravasation inflammation tenderness, injection site erythema, feeling cold, chest pressure sensation, chest discomfort, groin pain, chest tightness, general physical health deterioration, catheter related complication, change in thirst, feeling of body temperature change, death (incl. sudden), multi-organ failure, injection site haemorrhage, hernia (incl. hiatus), impaired healing, inflammation, injection site phlebitis, tenderness, ulcer, irritability, catheter site pain, sensation of foreign body
Investigations	Frequent Less frequent	Weight decreased, blood lactate dehydrogenase increased Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased,

		blood alkaline phosphatase increased, blood creatinine increased, blood urea increased, gamma-glutamyltransferase increased, blood amylase increased, liver function tests abnormal, red blood cell count decreased, white blood cell count decreased, blood bicarbonate decreased, heart rate irregular, C-reactive protein increased, blood phosphate decreased, weight increased
Injury and poisoning	Less frequent	Catheter related complications, post procedural pain, post procedural haemorrhage, burns, fall, contusion, transfusion reaction, fractures, rigors, face injury, joint injury, laceration, radiation injuries
Surgical and medical procedures	Less frequent	Macrophage activation

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

Overdosage has been associated with acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies, see section 5.3.

Management of overdose:

It is recommended that in the event of overdosage, patients should undergo careful haemodynamic monitoring, and hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents

ATC code: L01XX32

Pharmacological classification: A 26 Cytostatic agents.

Mechanism of action:

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and Nuclear Factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourogenesis, including cell growth and survival, angiogenesis, cell:cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

5.2 Pharmacokinetic properties

Absorption:

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mL respectively after the first dose. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1,0 mg/m^2 dose and 89 to 120 ng/mL for the 1,3 mg/m^2 dose.

Distribution:

The mean distribution volume of bortezomib was variable and ranged from 1659 litres to 3294 litres following single- or repeat-dose administration of 1,0 mg/m^2 or 1,3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma averaged 83 % over the concentration range 100 - 1000 mg/mL.

Biotransformation:

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and IA2. Bortezomib metabolism by CYP2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent.

Elimination:

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively, and ranged from 15 to 32 L/h and 18 to 32 L/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Pharmacokinetics in special patient groups

Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (% CV) clearance was 7,79 (25 %) L/hr/m^2, volume of distribution at steady-state was 834 (39 %) L/m^2, and the elimination half-life was 100 (44 %) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in paediatric patients was similar to that observed in adults.

The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment Mild hepatic impairment did not alter dose-normalised bortezomib AUC. However, the dose-normalised mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely (see Table 4).

Renal Impairment Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among patients with various degrees of renal impairment.

5.3 Preclinical safety data

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary (CHO) cells at concentrations as low as 3,125 µg/mL, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-foetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenia's, lymphoid tissue atrophy and haematopoietic bone marrow hypocellularity; peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment.

Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

Cardiovascular safety pharmacology studies in monkeys and dogs show that intravenous doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

VELBOR IV must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened:

24 months

Reconstituted solution:

The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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 a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

6.4 Special precautions for storage

Powder: Store at or below 25 ˚C.

Keep the vial in the carton until required for use.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

Clear 10 mL glass vial with grey rubber plug, aluminium seal with red flip off cap. Each vial is placed in an outer carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

General precautions

VELBOR IV is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELBOR IV SINCE NO PRESERVATIVE IS PRESENT.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. VELBOR IV lyophilised powder for solution for injection is for intravenous or subcutaneous use only. VELBOR IV should not be administered intrathecally.

Instructions for reconstitution

VELBOR IV must be reconstituted by a healthcare provider.

Intravenous injection:

The contents of each 10 mL vial must be reconstituted with 3,5 mL of sodium chloride 9 mg/mL normal (0,9 %) saline.

After reconstitution, each mL of solution contains 1 mg bortezomib.

Subcutaneous injection:

The contents of each 10 mL vial must be reconstituted with 1,4 mL of normal (0,9 %) saline.

After reconstitution, each mL of solution contains 2,5 mg bortezomib.

VELBOR IV must not be mixed with any other medicinal products except for normal (0,9 %) saline, sodium chloride injection USP.

The contents of each vial should be reconstituted with normal (0,9 %) saline according to the following instructions, based on route of administration:

	IV	**SC**
Volume of diluent (0,9 % Sodium Chloride) added to reconstitute one vial	3,5 mL	1,4 mL
Final concentration after reconstitution (mg/mL)	1,0 mg/mL	2,5 mg/mL

Dissolution is completed in less than 2 minutes. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. 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 product must be discarded.

Disposal

VELBOR IV is for single use only.

Any unused product or waste material should be disposed of appropriately.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

MC Pharma (Pty) Ltd

62 Constantia Avenue

Mnandi

0157

South Africa

8. REGISTRATION NUMBER

A50/26/0960

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2020

10. DATE OF REVISION OF THE TEXT

To be allocated