Applicant: Aurogen SA (Pty) Ltd
Product Name: DEVACAD
Dosage form and strength: Powder for solution for injection 3,5 mg

MODULE 1
1.3.1.1
~~**Date**: 16 February 2023~~
Date: 10 May 2023

1.3.1.1 Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DEVACAD powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEVACAD

Each vial contains 3,5 mg bortezomib (as a mannitol boronic ester).

Contains sugar: mannitol (35,0 mg)

After reconstitution, 1ml of solution for subcutaneous injection contains 2,5 mg bortezomib.

After reconstitution, 1ml of solution for intravenous injection contains 1mg bortezomib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEVACAD powder for solution for injection is indicated for:

- 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

DEVACAD 3,5 mg 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 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.

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

See section 6.6 for Reconstitution Instructions.

Monotherapy

Recommended dosage

The recommended starting dose of DEVACAD 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 DEVACAD.

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

There is limited data concerning re-treatment with DEVACAD.

Recommended dosage adjustments during treatment and re-initiation of treatment

DEVACAD 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 also section 4.4). Once the symptoms of the toxicity have resolved, DEVACAD 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 DEVACAD must be considered.

Patients who experience DEVACAD 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 DEVACAD only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for DEVACAD 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 DEVACAD treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate DEVACAD 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 DEVACAD

***** Based on dose modifications in phase II and III multiple myeloma studies.

Special populations

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

Patients with hepatic impairment:

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended DEVACAD dose. Patients with moderate or severe hepatic impairment should be started on DEVACAD 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 2).

Table 2: Recommended starting dose modification for DEVACAD 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	None
Moderate	> 1,5 x – 3 x ULN	Any	Reduce DEVACAD 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		

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

AST = aspartate aminotransferase, ULN = upper limit of the normal range.

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

Combination therapy

Recommended dosage

DEVACAD (bortezomib) powder for solution for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 3.

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

Table 3: Recommended dosage regimen for DEVACAD when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma

Twice weekly DEVACAD (Cycles 1 – 4)												
Week	1				2		3	4		5		6
DEVACAD (1,3 mg/m^2)	day 1			day 4	day 8	day 11	rest period	day 22	day25	day 29	day32	rest period
m (9 mg/m^2 P (60 mg/m^2)	day 1	day 2	day 3	day 4	-	-	rest period	-	-	-	-	rest period

Once weekly DEVACAD (Cycles 5 – 9)									
Week	1				2	3	4	5	6
DEVACAD (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	day 2	day 3	day 4	-	rest period	-	-	rest period

DEVACAD; m = melphalan; p = prednisone

Dose Management Guidelines for Combination Therapy

Dose modification and re-initiation of therapy when DEVACAD 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 4: Dose Modifications during Subsequent Cycles:

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle
• If the platelet count ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a DEVACAD dosing day (other than day 1)	DEVACAD should be withheld

If several DEVACAD doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	DEVACAD 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	DEVACAD therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, DEVACAD may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 g/m^2 to 0,7 mg/m^2). For DEVACAD related neuropathic pain and/or peripheral neuropathy, hold and/or modify DEVACAD as outlined in Table 1.

For additional information concerning melphalan and prednisone, refer to their respective professional information inserts.

Paediatric patients:

DEVACAD has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data becomes available.

Method of Administration

Administration precautions

There have been fatal cases of inadvertent intrathecal administration of DEVACAD.

DO NOT ADMINISTER DEVACAD INTRATHECALLY.

DEVACAD 3,5 mg

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 DEVACAD.

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.

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

4.3 Contraindications

Hypersensitivity to bortezomib, boron or to any of the excipients.

See section 6.1.

Acute diffuse infiltrative pulmonary and pericardial disease. When DEVACAD is given in combination with other medicines, refer to their Professional Information for additional contraindications.

4.4 Special warnings and precautions for use

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

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of DEVACAD. DEVACAD 3,5 mg powder for solution for injection is for intravenous or subcutaneous use.

DO NOT ADMINISTER DEVACAD INTRATHECALLY.

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with DEVACAD treatment. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration if anti-emetics and anti-diarrhoeals. Fluid and electrocyte replacements should be administered to prevent or treat dehydration. Cases of ileus have been uncommonly reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity

DEVACAD treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia).

However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of DEVACAD treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease, and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative

thrombocytopenia or neutropenia in any of the regimens studied. Platelet counts should be monitored prior to each dose of DEVACAD. Therapy should be withheld when the platelet count is < 25,000/µL, or in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µL (see sections 4.2 and 4.8). Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated

with thrombocytopenia, has been reported. 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 haematological toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

In the multiple myeloma study of DEVACAD vs dexamethasone, the mean platelet count nadir measured was approximately 40 % of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in Table 6. The incidence of significant bleeding events (≥ Grade 3) was similar on both the DEVACAD (4 %) and dexamethasone (5 %) arms.

Gastrointestinal and intracerebral haemorrhage, have been reported in association with DEVACAD treatment. Therefore, platelet counts should be monitored prior to each dose of DEVACAD. DEVACAD therapy should be withheld when the platelet count is < 25,000/µL or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µL (see section 4.2). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with DEVACAD. Platelet transfusion should be considered when clinically appropriate (see section 4.2).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of DEVACAD treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78 % of patients in the VcR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.2).

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with DEVACAD. In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with bortezomib + Melphalan + Prednisone compared with Melphalan + Prednisone~~.~~

The incidence of herpes zoster among patients in the study was 17 % for patients not administered antiviral prophylaxis compared to 3 % for patients administered antiviral prophylaxis.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with DEVACAD, 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 DEVACAD. Antiviral prophylaxis should be considered. Refer to the professional information inserts of rituximab for more information.

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 bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of DEVACAD. 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 DEVACAD if PML is diagnosed.

Peripheral neuropathy

Treatment with DEVACAD is very commonly associated with peripheral neuropathy, which 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 DEVACAD. 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, hyperaesthesia, hypoaesthesia, paraesthesia, discomfort, neuropathic pain or weakness. In the Phase 3 study comparing bortezomib IV vs SC the incidence of Grade ≥ 2 peripheral neuropathy events was 24 % for SC and 41 % for IV (p=0,0124). Grade ≥ 3 peripheral neuropathy occurred in 6 % of subjects in the SC treatment group, compared with 16 % in the IV

treatment group (p=0,0264) (see section 4.8). Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting DEVACAD subcutaneously.
Patients experiencing new or worsening peripheral neuropathy may require the dose, schedule or route of administration to SC to be modified (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible.
Improvement in, or resolution of, peripheral neuropathy was reported in 51 % of patients with

Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of bortezomib vs dexamethasone and 73 % of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase 2 studies, respectively.

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 undesirable 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

DEVACAD treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on DEVACAD (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with DEVACAD. Most patients required treatment for their

orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of DEVACAD. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to DEVACAD or DEVACAD may aggravate an underlying condition such as diabetic or amyloidotic 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 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.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving bortezomib. PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, DEVACAD should be discontinued.

Cardiac disorders

Development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

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 bortezomib (see section 4.8). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing DEVACAD therapy. In a clinical trial, two patients (out of 2) given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections 4.2 and 5.2).

Hepatic impairment

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

Hepatic reactions

Cases of hepatic failure have been reported in patients receiving bortezomib and concomitant medicines and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of DEVACAD (see section 4.8).

Tumour lysis syndrome

Because bortezomib is a cytotoxic medicine and can rapidly kill malignant plasma cells and MCL 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. These patients should be monitored closely and appropriate precautions taken.

Concomitant medicines

Patients should be closely monitored when given DEVACAD 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 hypoglycaemic (see section 4.5).

Potentially immunocomplex-mediated reactions

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

4.5 Interaction with other medicines and other forms of interactions

In vitro studies indicate that 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 metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug 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 % ($CI_{90\%}$ [1,032 to 1,772]) based on data from 12 patients. Therefore, patients should be closely monitored when given DEVACAD in combination with potent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. Therefore, the concomitant use of DEVACAD with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.

A drug-drug interaction study assessing the effect of melphalan-prednisone on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 17 % 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 hypoglycaemic. Patients on oral antidiabetic medicines receiving DEVACAD treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

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

Pregnancy

Safety in pregnancy has not been established.

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

Breastfeeding

Safety in lactation has not been established.

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

Fertility

There are no data on fertility.

4.7 Effects on ability to drive and use machines

DEVACAD may have a moderate influence on the ability to drive and use machines. DEVACAD may be associated with fatigue, dizziness, syncope and orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

The following undesirable effects included are considered to have at least a possible or probable causal relationship to DEVACAD in controlled clinical trials.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: frequent (≥ 1/10); less frequent (≥ 1/100, < 1/10); frequency unknown (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5: Adverse reactions in patients with Multiple Myeloma treated with DEVACAD in clinical trials and all post-marketing adverse reactions regardless of indication

System organ class	**Incidence**	**Adverse reaction**
Infections and infestations	Frequent	Herpes zoster (inc disseminated & ophthalmic), pneumonia, herpes simplex, sinusitis, nasopharyngitis, bronchitis
	Less frequent	Infection, bacterial infections, viral infections, sepsis (inc septic shock), bronchopneumonia, herpes virus infection, meningoencephalitis herpetic, bacteraemia (inc staphylococcal), hordeolum, influenza, cellulitis, device related infection, skin infection, ear infection, staphylococcal infection, tooth infection, fungal infection, meningitis (inc bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome

Neoplasms benign, malignant and unspecified	Less frequent	Neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia
	Less frequent	Pancytopenia, febrile neutropenia, coagulopathy, leukocytosis, lymphadenopathy, haemolytic anaemia, disseminated intravascular coagulation, thrombocytosis, hyperviscosity syndrome, platelet disorder NOS, thrombotic microangiopathy (inc thrombocytopenic purpura), Blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration
Immune system disorders	Less frequent	Angioedema, hypersensitivity, anaphylactic shock, amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Less frequent	Cushing's syndrome, hyperthyroidism, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutrition disorders	Frequent	Decreased appetite, dehydration, hypokalaemia, hyponatraemia, blood glucose abnormal, enzyme abnormality, hyperglycaemia
	Less frequent	Tumour lysis syndrome, failure to thrive, hypomagnesaemia, hypophosphataemia, hyperkalaemia, hypercalcaemia, hypernatraemia, uric acid abnormal, diabetes mellitus, fluid retention, hypocalcaemia, cachexia, hypoglycaemia,

		hypermagnesaemia, acidosis, electrolyte imbalance, fluid overload, hypochloraemia, hypovolaemia, hyperchloraemia, hyperphosphataemia, metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, gout, increased appetite, alcohol intolerance
Psychiatric disorders	Frequent	Mood disorders and disturbances, anxiety disorder, insomnia, confusion, depression
	Less frequent	Mental disorder, hallucination, psychotic disorder, restlessness, sleep disorders, agitation, irritability, abnormal dreams, suicidal ideation, adjustment disorder, delirium, libido decreased
Nervous system disorders	Frequent	Neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, paraesthesia, motor neuropathy, loss of consciousness (inc syncope), dizziness, dysgeusia, lethargy, headache, tremor
	Less frequent	Peripheral sensorimotor neuropathy, dyskinesia, cerebellar coordination and balance disturbances, memory loss (exc dementia), encephalopathy, posterior reversible encephalopathy syndrome, neurotoxicity, seizure disorders, post herpetic neuralgia, speech disorder, restless legs syndrome, migraine, sciatica, disturbance in attention, reflexes abnormal, parosmia, cerebral haemorrhage, Haemorrhage intracranial (inc subarachnoid), brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance,

		autonomic neuropathy, cranial palsy, paralysis, paresis, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder NOS, motor dysfunction, nervous system disorder NOS, radiculitis, drooling, hypotonia
Eye disorders	Frequent	Vision abnormal, eye pain
	Less frequent	Eye haemorrhage, eyelid infection*, chalazion, blepharitis, eye inflammation, diplopia, dry eye, eye irritation, lacrimation increased, eye discharge, eye swelling, conjunctivitis, corneal lesion, exophthalmos, retinitis, scotoma, eye disorder (inc. eyelid) NOS, dacryoadenitis acquired, photophobia, photopsia, optic neuropathy, different degrees of visual impairment (up to blindness)
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Dysacusis (inc tinnitus), hearing impaired (up to and inc deafness), ear discomfort, ear haemorrhage, vestibular neuronitis, ear disorder NOS
Cardiac disorders	Less frequent	Cardiac tamponade, cardio-pulmonary arrest, cardiac fibrillation (inc atrial), cardiac failure(inc left and right ventricular), dysrhythmia, tachycardia, palpitations, angina pectoris, pericarditis (inc pericardial effusion), cardiomyopathy, ventricular dysfunction, bradycardia, atrial flutter, myocardial infarction, atrioventricular block,

		cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, angina unstable, cardiac valve disorders, coronary artery insufficiency, sinus arrest
Vascular disorders	Frequent	Hypotension, orthostatic hypotension, hypertension, phlebitis, haematoma (including perirenal)
	Less frequent	Cerebrovascular accident, deep vein thrombosis, haemorrhage, thrombophlebitis (inc superficial), circulatory collapse (inc hypovolaemic shock), flushing, poor peripheral circulation, vasculitis, hyperaemia (inc ocular), peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, upper/lower respiratory tract infection, cough, rhinorrhoea
	Less frequent	Pulmonary embolism, pleural effusion, pulmonary oedema (inc acute), pulmonary alveolar haemorrhage, bronchospasm, chronic obstructive pulmonary disease, hypoxaemia, respiratory tract congestion, hypoxia, pleurisy, hiccups, dysphonia, wheezing, respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, 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
Gastrointestinal disorders	Frequent	Nausea and vomiting symptoms, diarrhoea, constipation, gastrointestinal haemorrhage (inc mucosal), dyspepsia, stomatitis, abdominal distension, oropharyngeal pain, abdominal pain (inc gastrointestinal and splenic pain), oral disorder, flatulence, hiccups, dry mouth
	Less frequent	Pancreatitis (inc chronic), haematemesis, lip swelling, gastrointestinal obstruction (inc small intestinal obstruction, ileus), abdominal discomfort, oral ulceration, enteritis, gastritis, gingival bleeding, gastro-oesophageal reflux disease, colitis (inc clostridium difficile), colitis ischaemic, gastrointestinal inflammation, dysphagia, irritable bowel syndrome, gastrointestinal disorder NOS, tongue coated, gastrointestinal motility disorder, salivary gland disorder, pancreatitis acute, peritonitis, tongue oedema, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma, gastrointestinal ulceration and perforation, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces
	Frequent	Hepatic enzyme abnormality

Hepatobiliary disorders	Less frequent	Hepatotoxicity (inc liver disorder), hepatitis, cholestasis, hypoproteinaemia, hyperbilirubinemia, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritis, dry skin, eczema, hyperhidrosis
	Less frequent	Erythema multiforme, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, dermatitis, hair disorder, petechiae, ecchymosis, skin lesion, purpura, skin mass, psoriasis, night sweats, decubitus ulcer, acne, blister, pigmentation disorder, skin reaction, Jessner's lymphocytic infiltration, palmar-plantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction, seborrhoea, cold sweat, skin disorder NOS, erythrosis, skin ulcer, nail disorder
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal pain, myalgia, muscle spasms, pain in extremity, muscular weakness
	Less frequent	Muscle twitching, joint swelling, arthritis, joint stiffness, myopathies, sensation of heaviness, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, pain in jaw, bone disorder, musculoskeletal and connective tissue infections and inflammations, synovial cyst
	Frequent	Renal impairment, dysuria

Renal and urinary disorders	Less frequent	Renal failure acute, renal failure chronic, urinary tract infection, urinary tract signs and symptoms, Haematuria, urinary retention, micturition disorder, proteinuria, azotaemia, oliguria, pollakiuria, bladder irritation
Reproductive system and breast disorders	Less frequent	Vaginal haemorrhage, genital pain, erectile dysfunction, testicular disorder, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders	Less frequent	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions	Frequent	Pyrexia, fatigue, asthenia, oedema (Inc peripheral), chills, pain, malaise
	Less frequent	General physical health deterioration, face oedema, injection site reaction, mucosal disorder, chest pain, gait disturbance, feeling cold, extravasation, catheter related complication, change in thirst, chest discomfort, feeling of body temperature change, injection site pain, death (inc sudden), multi-organ failure, injection site haemorrhage, hernia (inc hiatus), impaired healing, inflammation, injection site phlebitis, tenderness, ulcer, irritability, non-cardiac chest pain, catheter site pain, sensation of foreign body
Investigations	Frequent	Weight decreased

	Less frequent	Hyperbilirubinaemia, protein analyses abnormal, weight increased, blood test abnormal, C-reactive protein increased, blood gases abnormal, Electrocardiogram abnormalities (inc QT prolongation), International normalised ratio abnormal, gastric pH decreased, platelet aggregation increased, Troponin I increased, virus identification and serology, urine analysis abnormal
Injury, poisoning and procedural complications	Less frequent	Fall, contusion, transfusion reaction, fractures, rigors, face injury, joint injury, Burns, laceration, procedural pain, radiation injuries
Surgical and medical procedures	Less frequent	Macrophage activation
NOS = not otherwise specified		

Summary of Clinical Trials in patients with previously untreated multiple myeloma:

The following table describes safety data from 340 patients with previously untreated multiple myeloma who received DEVACAD (1,3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective phase III study.

Table 6: Treatment Emergent Drug-Related Adverse Events reported in ≥ 10 % of patients treated with DEVACAD in combination with melphalan and prednisone

	----------Vc-MP----------		
	(n = 340)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥ 4
Blood and Lymphatic System disorders			
Thrombocytopenia	164 (48)	60 (18)	57 (17)
Neutropenia	160 (47)	101 (30)	33 (10)
Anaemia	109 (32)	41 (12)	4 (1)
Leukopenia	108 (32)	64 (19)	8 (2)
Lymphopenia	78 (23)	46 (14)	17 (5)
Gastrointestinal Disorders			
Nausea	134 (39)	10 (3)	0
Diarrhoea	119 (35)	19 (6)	2 (1)
Vomiting	87 (26)	13 (4)	0
Constipation	77 (23)	2 (1)	0
Abdominal Pain Upper	34 (10)	1 (< 1)	0
Nervous System Disorders			
Peripheral Neuropathy	156 (46)	42 (12)	2 (1)
Neuralgia	117 (34)	27 (8)	2 (1)
Paraesthesia	42 (12)	6 (2)	0

General Disorders and Administration			
Site Conditions			
Fatigue	85 (25)	19 (6)	2 (1)
Asthenia	54 (16)	18 (5)	0
Pyrexia	53 (16)	4 (1)	0
Infections and Infestations			
Herpes Zoster	39 (11)	11 (3)	0
Metabolism and Nutrition Disorders			
Anorexia	64 (19)	6 (2)	0
Skin and Subcutaneous Tissue			
Disorders			
Rash	38 (11)	2 (1)	0
Psychiatric Disorders			
Insomnia	35 (10)	1 (< 1)	0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9 Overdose

One case of overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported with bortezomib as in DEVACAD. Overdosage was associated with acute onset of symptomatic hypotension and the patient subsequently died. 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

PHARMACOLOGICAL CLASSIFICATION

A 26 Cytostatic agents

Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32

Mechanism of action

Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. At 10 µM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome

inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible. Bortezomib mediated proteasome inhibition affects cancer 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 tumourigenesis, 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 pro-apoptotic 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 11 patients with multiple myeloma and creatinine clearance values greater than 50 mL/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively. 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. Following an intravenous bolus or subcutaneous injection of a 1,3 mg/m^2 dose to patients with multiple myeloma (n = 14 in the

intravenous group, n = 17 in the subcutaneous group), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. The C_{max} after subcutaneous administration (20,4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0,99 and 90 % confidence intervals were 80,18 % - 122,80 %.

Distribution

The mean distribution volume (V_d) of bortezomib ranged from 1,659 L to 3,294 L following single-or repeated-dose intravenous 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. Over a bortezomib concentration range of 100 – 1000 mg/mL, the *in vitro* protein binding averaged 83 % in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.

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 1A2. 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.

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 following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Special Populations

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed. Including 51 patients primarily with solid tumours and varying degrees of hepatic impairment at bortezomib doses ranging from 0,5 to 1,3 mg/m^2.

When compared to patients with normal hepatic function, 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 closely monitored (see Table 2 and section 4.2).

Renal impairment

A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mL/min/1,73 m^2, n = 12), Mild (CrCL = 40 – 59 mL/min/1,73m^2, n = 10), Moderate (CrCL = 20 – 39 mL/min/1,73 m^2, n = 9), and Severe (CrCL < 20 mL/min/1,73 m^2, n = 3). A group of dialysis patients who were dosed after dialysis was also included in the study (n = 8). Patients were administered intravenous doses of 0,7 to 1,3 mg/m^2 of DEVACAD twice weekly. Exposure of DEVACAD (dose-normalised AUC and Cmax) was comparable among all the groups (see section 4.2).

Age, Gender and Race

The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 – 16 years old) with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML). 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol, tert-butanol, Water for injection

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Unopened vial:

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

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5. Nature and contents of container

DEVACAD is supplied as a single-use 10 mL Type-I clear glass tubular vial stoppered with grey rubber stopper and sealed with an aluminium seal having a Taxim Blue PP disc. The vial is packed in a pre-printed carton with a professional information insert/patient information leaflet.

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

For single use only

DEVACAD is a cytotoxic agent. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

Reconstitution Instructions

DEVACAD 3,5 mg is for IV or SC use.

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.

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

DEVACAD is provided as a lyophilised powder in the form of a mannitol boronic ester. When reconstituted, the mannitol ester is in equilibrium with its hydrolysis product, the monomeric boronic acid.

Reconstitution for intravenous administration

Prior to use, the contents of each 10 mL vial must be reconstituted with 3,5 mL of normal (0,9 %) saline.

DEVACAD must not be mixed with any other medicinal products except for normal (0,9 %) saline, Sodium Chloride Injection, USP.

Table 7: The contents of each vial should be reconstituted only with normal (0,9 %) saline according to the following instructions based on route of administration:

	IV	**SC**
	3,5 mg bortezomib	**3,5 mg bortezomib**

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.

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is 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 prior to administration, with a maximum of 8 hours in the syringe.

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

54/26/0082

9. DATE OF FIRST AUTHORISATION

20 JUNE 2023