1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PROFESSIONAL INFORMATION HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

SPALBORT 3,5 mg (Lyophilised powder for solution for Injection for intravenous and subcutaneous use)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each vial contains 3,5 mg bortezomib.

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

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

Contains sugar: 35 mg mannitol per vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SPALBORT 3,5 mg is a white to off-white, lyophilised powder or cake for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPALBORT 3,5 mg for injection 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

SPALBORT 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.

SPALBORT 3,5 mg should not be given by other routes. Intrathecal administration has resulted in death.

See Reconstitution Instructions below.

Posology

Monotherapy

Recommended dosage

The recommended starting dose of **SPALBORT 3,5 mg** 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 **SPALBORT 3,5 mg**.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of **SPALBORT 3,5 mg** beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of **SPALBORT 3,5 mg** therapy.

There is limited data concerning re-treatment with bortezomib such as in **SPALBORT 3,5 mg**.

Recommended dosage adjustments during treatment and re-initiation of treatment

SPALBORT 3,5 mg 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, **SPALBORT 3,5 mg** treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2 or 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 **SPALBORT 3,5 mg** must be considered.

Patients who experience **SPALBORT 3,5 mg** 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 **SPALBORT 3,5 mg** only after careful risk/benefit assessment.

Table 1: Recommended dose modifications for SPALBORT 3,5 mg related Neuropathic Pain and/or Peripheral Sensory Neuropathy.

Severity of peripheral neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or	No action

loss of reflexes) with no pain or loss of function	
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 **SPALBORT 3,5 mg** treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate **SPALBORT 3,5 mg** 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 **SPALBORT 3,5 mg**

Special populations

Pediatric patients

SPALBORT 3,5 mg has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data become available.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly.

Patients with Renal Impairment

The pharmacokinetics of **SPALBORT 3,5 mg** are not influenced by the degree of renal impairment. Therefore, dosing adjustments of **SPALBORT 3,5 mg** are not necessary for patients with renal insufficiency. Since dialysis may reduce **SPALBORT 3,5 mg** concentrations, **SPALBORT 3,5 mg** 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 **SPALBORT 3,5 mg** dose. Patients with moderate to severe hepatic impairment should be started on **SPALBORT 3,5 MG** at a reduced dose of

0,7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² may be considered based on patient tolerance (see Table 2).

Table 2: Recommended Starting Dose Modification for SPALBORT 3,5 mg 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 **SPALBORT 3,5 mg** to 0,7 mg/m² in the first cycle. Consider dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

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).

Administration

Administration Precautions

There have been fatal cases of inadvertent intrathecal administration of bortezomib.
DO NOT ADMINISTER SPALBORT 3,5 mg INTRATHECALLY.

SPALBORT 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 **SPALBORT 3,5 mg**.

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 **SPALBORT 3,5 mg** injection subcutaneously, a less concentrated **SPALBORT 3,5 mg** solution (1 mg/ml instead of 2,5 mg/ml) may be administered subcutaneously, or changed to IV injection.

Combination Therapy

Recommended Dosage

SPALBORT 3,5 mg (bortezomib) 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, **SPALBORT 3,5 mg** is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, **SPALBORT 3,5 mg** is administered once weekly (days 1, 8, 22 and 29).

Table 3: Recommended Dosage Regimen for SPALBORT 3,5 mg when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma

	Twice Weekly SPALBORT 3,5 mg (Cycles 1-4)											
Week	1				2		3	4		5		6
Vc (1,3 mg/m^2)	Day 1			Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	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 SPALBORT 3,5 mg (Cycles 5-9)												
Week	1				2		3	4		5		6
Vc (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

Vc = **SPALBORT 3,5 mg**; m = melphalan, p=prednisone

Dose Management Guidelines for Combination Therapy

*Dose modification and re-initiation of therapy when **SPALBORT 3,5* **mg** *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 absolute neutrophil count (ANC) should be ≥ 1,0 x 10^9/L

- Non-haematological toxicities should have resolved to Grade 1 or baseline (See table 4 below)

Table 4: Dose Modifications during Subsequent Cycles:

Toxicity	Dose modification or delay
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropaenia or thrombocytopaenia, or thrombocytopaenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.
• If platelet count ≤ 30 × 10^9/L or ANC ≤ 0,75 x 10^9/L	**SPALBORT 3,5 mg** dose should be withheld
If several **SPALBORT 3,5 mg** doses in a cycle are withheld (≥ 3 doses during twice weekly administration	**SPALBORT 3,5 mg** dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m2
Grade ≥ 3 non-haematological toxicities	**SPALBORT 3,5 mg** therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, **SPALBORT 3,5 mg** may be reinitiated 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 **SPALBORT 3,5** -related neuropathic pain and/or peripheral neuropathy, hold and/or modify **SPALBORT 3,5 mg** as outlined in Table 2.

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

Method of administration:

SPALBORT 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.

4.3 Contraindications

Hypersensitivity to bortezomib, or to any of the excipients of **SPALBORT 3,5 mg** (see section 6.1 for list of excipients).

Severe hepatic impairment.

Acute diffuse infiltrative pulmonary and pericardial disease.

When SPALBORT 3.5 mg 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.

There have been fatal cases of inadvertent intrathecal administration of **SPALBORT 3,5 mg**.

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

DO NOT ADMINISTER SPALBORT 3,5 mg INTRATHECALLY.

Herpes Zoster Virus Reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with **SPALBORT 3,5 mg**. In studies in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with Bortezomib, Melphalan and Prednisone (VcMP) compared with Melphalan + Prednisone.

Hepatitis B virus (HBV) reactivation and infection:

When rituximab is administered in combination with **SPALBORT 3,5 mg**, 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 **SPALBORT 3,5 mg**. Antiviral prophylaxis should be considered.

Progressive multifocal leukoencephalopathy (PML):
Very rare 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 bortezomib. 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 **SPALBORT 3,5 mg** if PML is diagnosed.

Patients with mantle cell lymphoma:
Safety data for patients with mantle cell lymphoma was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopaenia, neutropaenia, anaemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.
Based on the integrated safety database from 256 patients with relapsed and/or refractory multiple myeloma, the following special precautions are suggested:
Overall, the safety profile of patients treated with bortezomib in monotherapy was similar to that observed in patients treated with bortezomib in combination with melphalan and prednisone.

Laboratory Tests
Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with **SPALBORT 3,5 mg**.

Gastrointestinal toxicity
Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with **SPALBORT 3,5 mg** 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 anti-emetics and anti-diarrhoeals. 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

SPALBORT 3,5 mg treatment is very commonly associated with haematological toxicities (thrombocytopaenia and neutropaenia). However, febrile neutropaenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopaenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of **SPALBORT 3,5 mg** treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet decrease and recovery remained consistent over the 8 cycles of twice weekly dosing and there was no evidence of cumulative thrombocytopaenia. The mean platelet count nadir measured was approximately 40 % of baseline. Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopaenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopaenia was related to pre-treatment platelet count. Platelet counts should be monitored prior to each dose of **SPALBORT 3,5 mg**. Therapy should be held when the platelet count is < 25,000/µL and re-initiated at a reduced dose after resolution (see section4.8). 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 thrombocytopaenic patients at high risk of bleeding.

Peripheral Neuropathy

SPALBORT 3,5 mg 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 **SPALBORT 3,5 mg**. 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 or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of **SPALBORT 3,5 mg** 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 a single medicine phase III multiple myeloma study and 71 % of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase II 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.

Seizures

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

Hypotension

SPALBORT 3,5 mg treatment is commonly associated with orthostatic/postural hypotension. Most patients require treatment for their orthostatic hypotension. Patients with orthostatic hypotension may 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 **SPALBORT 3,5 mg** or **SPALBORT 3,5 mg** may aggravate an underlying condition such as diabetic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products 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 medicinal products, 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 in clinical trials; causality has not been established.

Patients using angiotensin converting enzyme inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during **SPALBORT 3,5 mg** treatment.

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 **(SPALBORT 3,5 mg)**. 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.

In a clinical trial, the first two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion in combination with daunorubicin and bortezomib **(SPALBORT 3,5 mg)** for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy. The trial was discontinued subsequently.

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, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of **SPALBORT 3,5 mg**. There is limited re-challenge information in these patients.

Hepatic Impairment

SPALBORT 3,5 mg is metabolised by liver enzymes (see section 5.2). **SPALBORT 3,5 mg** exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with **SPALBORT 3,5 mg** at reduced starting doses and closely monitored for toxicities (see section 4.2).

Tumour lysis syndrome

Because **SPALBORT 3,5 mg** is a cytotoxic medicine 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, dysrrhythmias and syncope. These patients should be monitored closely and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by **SPALBORT 3,5 mg** 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. **SPALBORT 3,5 mg** should be discontinued if severe reactions occur.

SPALBORT 3,5 mg contains mannitol and may have a laxative effect.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been reports of RPLS in patients receiving **SPALBORT 3,5 mg**. RPLS 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 RPLS, discontinue **SPALBORT 3,5 mg**.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies indicate that **SPALBORT 3,5 mg** 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 **(SPALBORT 3,5 mg)** the CYP2D6**,** poor metaboliser phenotype is not expected to affect the overall disposition of **SPALBORT 3,5 mg**.

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of **SPALBORT 3,5 mg**, showed a bortezomib AUC mean increase of 35 %, based on data from 12 patients. Therefore, patients should be monitored closely when given **SPALBORT 3,5 mg** in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir, chloramphenicol, clarithromycin).

In an interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of **SPALBORT 3,5 mg,** there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

An interaction study assessing the effect of rifampicin a potent CYP3A4 inducer, on the pharmacokinetics of **SPALBORT 3,5 mg** showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. The concomitant use of **SPALBORT 3,5 mg** 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. In the same interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

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

An interaction study assessing the effect of melphalan-prednisone on **SPALBORT 3,5 mg** 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 **SPALBORT 3,5 mg** 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.

Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 3 months following **SPALBORT 3,5 mg** therapy.

If **SPALBORT 3,5 mg** is used during pregnancy, or if the patient becomes pregnant while receiving **SPALBORT 3,5 mg**, the patient needs to be informed of potential for hazards to the foetus.

It is not known whether **SPALBORT 3,5 mg** is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from mothers on **SPALBORT 3,5 mg**, women should not breastfeed their infants while receiving **SPALBORT 3,5 mg**.

4.7 Effects on ability to drive and use machines

SPALBORT 3,5 mg may have a moderate influence on the ability to drive and use machines. **SPALBORT 3,5 mg** 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

The following undesirable effects included are considered to have at least a possible or probable causal relationship to **SPALBORT 3,5 mg**

Infections and infestations

Frequent: Herpes zoster (including disseminated). Pneumonia, herpes simplex, fungal infection.

Less Frequent: Sepsis, bacteraemia, bronchopneumonia, cytomegalovirus infection, influenza, herpes virus infection, meningoencephalitis herpetic, hordeolum, influenza, cellulitis, device related infection, skin infection, ear infection, staphylococcal infection, tooth infection, meningitis (incl bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome

Blood and lymphatic system disorders

Frequent: Thrombocytopaenia, neutropaenia, anaemia***.*** Leukopaenia, lymphopaenia***.***

Less Frequent: Pancytopenia, febrile neutropenia, coagulopathy, leukocytosis, lymphadenopathy, haemolytic anaemia, disseminated intravascular coagulation, thrombocytosis, hyperviscosity syndrome, platelet disorder, thrombocytopenic purpura, blood disorder, haemorrhagic diathesis, lymphocytic infiltration, thrombotic microangiopathy (including thrombocytopenic purpura)

Immune system disorders

Frequency unknown: Immunocomplex mediated hypersensitivity, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis.

Less frequent: Angioedema, hypersensitivity, anaphylactic shock, amyloidosis, Type III-immune complex mediated reactions

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, hypocalcaemia, enzyme abnormality.

*Less Frequent**:*** Tumour lysis syndrome, failure to thrive, hypomagnesaemia, hypophosphataemia, hyperkalaemia, hypercalcaemia, hypernatraemia, uric acid abnormal, diabetes mellitus, fluid retention, 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: Confusion, depression, insomnia, anxiety, mood disorders and disturbances, sleep disorders and disturbances.

Less Frequent: Mental disorder, hallucination, psychotic disorder, confusion, restlessness, suicidal ideation, adjustment disorder, delirium, libido decreased.

Nervous system disorders

Frequent: Neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, motor neuropathy, loss of consciousness (incl syncope), dizziness, dysgeusia, lethargy, headache

Less Frequent: Tremor, peripheral sensorimotor neuropathy, dyskinesia, cerebellar coordination and balance disturbances, memory loss (excl 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 (incl 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, motor dysfunction, nervous system disorder, radiculitis, drooling, hypotonia, Guillain-Barré syndrome, demyelinating polyneuropathy.

Eye disorders

Frequent: Vision blurred, conjunctivitis, eye swelling.

Less Frequent: Eye haemorrhage, abnormal vision, keratitis sicca, eye discharge, eye pain, photophobia, photopsia,optic neuropathy,different degrees of visual impairment (up to blindness), eye irritation, lacrimation increased, conjunctival hyperaemia, retinitis,scotoma,exophthalmos,corneal lesion,eyelid infection,eye inflammation,diplopia.

Ear and labyrinth disorders

Frequent: Vertigo.

Less Frequent: Deafness, tinnitus, hypoacusis, hearing impaired, ear discomfort,vestibular neuritis, ear disorder.

Cardiac disorders

Less Frequent: Cardiac arrest, cardiogenic shock, myocardial infarction, unstable angina pectoris, development or exacerbation of congestive heart failure (see section 4.4), cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, complete atrioventricular block, tachycardia, sinus tachycardia, supraventricular tachycardia, dysrhythmia, atrial fibrillation, palpitations.

Frequency unknown: New onset of decreased left ventricular ejection fraction (see section 4.4).

Vascular disorders

Frequent: Hypotension, orthostatic and postural hypotension (see section 4.4), phlebitis, haematoma, hypertension.

Less Frequent: Cerebral haemorrhage, vasculitis**,** cerebrovascular accident, pulmonary hypertension, petechiae, ecchymosis, purpura, vein discolouration, distended vein, wound hemorrhage, flushing, hot flushes.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea. Exertional dyspnea, epistaxis, cough, rhinorrhoea.

Less Frequent: Respiratory arrest, hypoxia, pulmonary congestion, pleural effusion, asthma, respiratory alkalosis, tachypnoea, wheezing, nasal congestion, hoarseness, rhinitis, hyperventilation, orthopnoea, chest wall pain, sinus pain, throat tightness, productive cough.

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: Acute pancreatitis, paralytic ileus, antibiotic associated colitis, colitis, haematemesis, haemorrhagic diarrhoea, 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, coated tongue, tongue discolouration, faecal impaction.

Hepatobiliary disorders

Frequent: Hepatic enzyme abnormality

Less Frequent: Hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia**.**

Skin and subcutaneous tissue disorders

Frequent: Rash. Periorbital oedema, urticaria, pruritic rash, pruritus, erythema, increased sweating, dry skin, eczema.

Less Frequent: Vasculitic rash (including leukocytoclastic vasculitis), erythematous rash, photosensitivity reaction, contusion, generalised pruritus, macular rash, papular rash, psoriasis, generalised rash, eyelid oedema, face oedema, dermatitis, alopecia, nail disorder, skin discolouration, atopic dermatitis, abnormal hair texture, heat rash, night sweats, pressure sore, ichthyosis, skin nodule.

Musculoskeletal and connective tissue 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.

Renal and urinary disorders

Frequent: Renal impairment, dysuria.

Frequency unknown: Acute renal failure, renal failure, oliguria, renal colic, haematuria, proteinuria, urinary retention, urinary frequency, difficulty in micturition, loin pain, urinary incontinence, micturition urgency.

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

General disorders and administration site conditions

Frequent: Fatigue, pyrexia. Asthenia, weakness, lethargy, rigors, malaise, influenza like illness, peripheral oedema, chest pain, pain, oedema.

Less frequent: 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.

Investigations

Frequent: Decreased weight, increased blood lactate dehydrogenase.
Less frequent: 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, abnormal liver function tests, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, increased C-reactive protein, decreased blood phosphate, increased weight.

Injury, poisoning and procedural complications
Less frequent: Catheter related complications, post procedural pain, post procedural haemorrhage, burns.

Clinically significant adverse reactions are listed here if they have not been reported above.

Blood and lymphatic system disorders
Disseminated intravascular coagulation.
Cardiac Disorders
Atrioventricular bock complete, cardiac tamponade.
Ear and labyrinth disorders
Deafness bilateral.
Eye disorders
Ophthalmic herpes,optic neuropathy, blindness.
Gastrointestinal Disorders
Ischaemic colitis, acute pancreatitis.
Intestinal obstruction.
Infections and infestations
Herpes meningoencephalitis, septic shock, progressive multifocal leukoencephalopathy.
Immune System Disorders
Angioedema.
Nervous System Disorders
Encephalopathy, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome.
Respiratory, thoracic and mediastinal disorders
Acute diffuse infiltrative pulmonary disease (see section 4.4), pulmonary hypertension.
Skin and subcutaneous tissue disorders
Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).

Acute febrile neutrophilic dermatosis (Sweet's syndrome).

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 Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage was associated with acute onset of symptomatic hypotension and thrombocytopenia 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

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32.

Bortezomib is a selective proteasome inhibitor. It specifically inhibits 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 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.

5.2 Pharmacokinetic properties

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. The mean elimination half-life 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.

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 1A2. Bortezomib metabolism by CYP 2D6 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. The pathways of elimination of bortezomib have not been characterised in humans.

Special populations:

Age, Gender and Race

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

Hepatic impairment:

Mild hepatic impairment did not alter dose-normalised bortezomib AUC. 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 section 4.2).

Renal impairment:

Bortezomib exposure is comparable in patients with various (mild, moderate to severe) degrees of renal impairment (see section 4.2)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, pyrogen free

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Unopened vial

3 years

Reconstituted solution

The reconstituted solution should be used immediately after preparation.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the vial in the outer carton in order to protect from light.

KEEP OUT OF REACH OF CHILDREN.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

6.5 Nature and contents of container

Clear single use 10 ml Type I glass vial sealed with 20 mm grey bromobutyl rubber stopper and Aluminium flip-off seal of purple color button. 1 vial in unit carton

6.6 Special precautions for disposal of a used medicine and other handling

Instructions for use and handling and disposal

For single use only.

SPALBORT 3,5 mg 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 SPALBORT 3,5 mg SINCE NO PRESERVATIVE IS PRESENT.

SPALBORT 3,5 mg 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

The contents of each 10 ml vial must be reconstituted with 3,5 ml of normal (0,9 %) saline.

SPALBORT 3,5 mg must not be mixed with any other medicinal products except for normal (0,9 %) saline, Sodium Chloride Injection, USP.

Table 5: 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. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 30° C stored in the original vial and/or a syringe prior to administration, with a maximum of 8 hours in the syringe at 30° C.

The reconstituted/ diluted solution is stable for up to 15 days when stored at 2 to 8°C in the vial/syringe.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd
Unit 1, 96 Hartley Road
Durban. 4091

8 REGISTRATION NUMBER(S)

55/26/0759

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 August 2023

10 DATE OF REVISION OF THE TEXT