Applicant/PHRC: ***Hetero Drugs South Africa (Pty) Ltd***

Product proprietary name: ***BORTIV 1 mg/0.4 ml, 2.5 mg/ml & 3.5 mg/1.4 ml***

Dosage form and strength: ***Solution for Injection.***
Each ml contains 2,5 mg of Bortezomib.

PROFESSIONAL INFORMATION FOR BORTIV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BORTIV 1 mg/0,4 ml; 2,5 mg/1 ml & 3,5 mg/1,4 ml (Solution for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BORTIV 1 mg/0,4 ml; 2,5 mg/1 ml & 3,5 mg/1,4 ml

Each mL contains 2,5 mg of Bortezomib

Contains sugar: 25 mg/mL of Mannitol

For a full list of excipients, (see Section 6.1)

3. PHARMACEUTICAL FORM

Solution for Injection

Clear colorless to light yellow solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BORTIV is indicated for:

Multiple Myeloma

- As monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.
- In combination with dexamethasone, or with dexamethasone and thalidomide, for the induction

treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation.

- In combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Mantle Cell Lymphoma

- 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.
- Treatment for newly diagnosed mantle cell lymphoma (MCL) in adults, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Posology

BORTIV 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.

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

Monotherapy

Recommended dosage

The recommended starting dose of **BORTIV** 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 lapse between consecutive doses of **BORTIV**.

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

Recommended dosage adjustments during treatment and re-initiation of treatment

BORTIV treatment must be withheld at the onset of any grade 3 non-haematological or any grade 4 haematological toxicities, excluding neuropathy as discussed below (see section 4.4). Once the symptoms of the toxicity have resolved, **BORTIV** 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 0,7mg/m^2). If toxicity is not resolved or if it recurs at the lowest dose, discontinuation of **BORTIV** must be considered.

Patients who experience **BORTIV** 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 **BORTIV** only after careful assessment.

Table 1: Recommended* dose modifications for BORTIV related neuropathic pain and /or peripheral sensory neuropathy

Severity of peripheral neuropathy	**Modification of dose and regimen**
Grade 1 (asymptomatic, paraesthesia, weakness and/or loss of reflex) with no pain or loss of function	No action
Grade 1 with pain or grade 2 (moderate symptoms, interfering with function but not activities of daily living)	Reduce to 1,0 mg/m^2 or Change **BORTIV** treatment schedule to 1,3 mg/m^2 once per week
Grade 2 with pain or grade 3 (severe symptoms, interfering with activities of daily living)	Withhold **BORTIV** treatment until symptoms of toxicity have resolved. When toxicity resolves re-

	initiate **BORTIV** treatment and reduce dose to 0,7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (life threatening consequences, sensory neuropathy which is disabling or motor neuropathy that is life- threatening or leads to paralysis)	Discontinue **BORTIV**

Combination therapy

Previously Untreated Multiple Myeloma - Patients who are Not Eligible for Stem Cell Transplantation

Recommended dosage in Combination with Melphalan and Prednisone

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

Table 2: Recommended dosage regimen for BORTIV when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma who are not eligible for stem cell transplantation:

Twice weekly BORTIV (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 BORTIV (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 = **BORTIV**; m = melphalan; p = prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone:

Dose modification and re-initiation of therapy when **BORTIV** 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 x10^9/ℓ.
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Table 3: Dose modifications during subsequent cycles:

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
If prolonged Grade 4 neutropenia or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle
If platelet count ≤ 30 x 10^9/ℓ or ANC ≤ 0,75 x 10^9/ℓ on a **BORTIV** dosing day (other than day 1)	**BORTIV** dose should be withheld
If several **BORTIV** doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration	**BORTIV** 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	**BORTIV** therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, **BORTIV** 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 **BORTIV** – related neuropathic pain and/or peripheral neuropathy, hold and/or modify **BORTIV** as outlined in Table 1

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

Previously Untreated Multiple Myeloma – Patients who are Eligible for Stem Cell Transplantation

Recommended Dosage

The recommended starting dose of **BORTIV** in combination with other medicines used for the treatment of multiple myeloma is 1,3 mg/m2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10-18 days, which is considered a treatment cycle. Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of **BORTIV**.

For **BORTIV** dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (Table 1) above.

For dosing instructions for other medicines combined with **BORTIV**, see their respective professional information leaflets.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin

For **BORTIV** dosage and dose modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the **BORTIV** 3-week regimen as a 1-hour intravenous infusion administered after the **BORTIV** injection. For additional information concerning pegylated liposomal doxorubicin, see respective professional information leaflet.

Recommended Dosage in Combination with Dexamethasone

For **BORTIV** dosage and dose modifications, see Monotherapy.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, **BORTIV** administration.

For additional information concerning dexamethasone, see respective professional information leaflet

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with **BORTIV** (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to Monotherapy for dosing schedule.

Previously Untreated Mantle Cell Lymphoma

Recommended Dosage in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

For **BORTIV** dosage, see Monotherapy. Six **BORTIV** cycles are administered. For patients with a response first documented at Cycle 6, two additional **BORTIV** cycles are recommended.

The following medicines are administered on Day 1 of each **BORTIV** 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m2, cyclophosphamide at 750 mg/m2, and doxorubicin at 50 mg/m2. Prednisone is administered orally at 100 mg/m2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be ≥ 100 x 109/L and absolute neutrophil count (ANC) should be ≥ 1,5 x 109/L
- Haemoglobin should be ≥ 8 g/dL (≥ 4,96 mmol/L)
- Non-haematologic toxicity should have recovered to Grade 1 or baseline

BORTIV treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 3 haematological toxicities, excluding neuropathy (see also section 4.4). For dose adjustments, see Table 4 below.

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. Platelet transfusion for the treatment of thrombocytopenia should be considered

when clinically appropriate.

Table 4: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x 10^9/L	BORTIV therapy should be withheld for up to 2 weeks until the patient has an ANC ≥0,75 x 10^9/L and a platelet count ≥25 x10^9/L • If, after BORTIV has been held, the toxicity does not resolve, as defined above, then BORTIV must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, BORTIV 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).
If platelet counts < 25 x 10^9/L. or ANC< 0,75 x 10^9/L on a BORTIV dosing day (other than Day 1)	BORTIV dose should be withheld

Grade ≥3 non-haematological toxicities	BORTIV therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BORTIV 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 BORTIV-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTIV as outlined in Table 1.

Special populations

Paediatric patients

BORTIV 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 (see section 4.8).

Patients with renal impairment

The pharmacokinetics of **BORTIV** are not influenced by in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 mL/min/1,73 m^2). Therefore, dosing adjustments of **BORTIV** are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce **BORTIV** concentrations, **BORTIV** 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 **BORTIV** dose. Patients with moderate or severe hepatic impairment should be started on

BORTIV 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 5: Recommended starting dose modification for BORTIV 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 **BORTIV** to 0,7 mg/m^2 in the first cycle. Consider dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 X ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

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

Method of administration

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

Administration Precautions

There have been fatal cases of inadvertent intrathecal administration of **BORTIV**.

BORTIV IS FOR INTRAVENOUS USE ONLY.

DO NOT ADMINISTER BORTIV INTRATHECALLY.

Intravenous injection:

The reconstitution 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 **BORTIV**

Subcutaneous injection:

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

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

4.3 Contraindications

- Hypersensitivity to any of the ingredients of bortezomib, or any of the ingredients of **BORTIV**, including the excipients listed in section 6.1.
- Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

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

There have been fatal cases of inadvertent intrathecal administration of **BORTIV**.

BORTIV is for IV or SC use only.

DO NOT ADMINISTER BORTIV INTRATHECALLY.

Herpes Zoster Virus Reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with **BORTIV**. Patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with **BORTIV**, melphalan and prednisone (VcMP)

Patients with mantle cell lymphoma

Safety data for patients with mantle cell lymphoma were evaluated in a phase 2 study, which included 155 patients treated with **BORTIV** at the recommended dose of 1,3 mg/m^2. The safety profile of **BORTIV** in these patients 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 **BORTIV** in monotherapy was similar to that observed in patients treated with **BORTIV** in combination with melphalan and prednisone.

Laboratory Tests

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

Gastrointestinal toxicity

Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with **BORTIV** 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

BORTIV treatment is very commonly associated with haematological toxicities (thrombocytopenia and neutropenia). 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 **BORTIV** 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 thrombocytopenia. The mean platelet count nadir measured was approximately 40 % of baseline. Severe bleeding, including CNS and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count (see table 6). Platelet counts should be monitored prior to each dose of **BORTIV**. Therapy should be held when the platelet count is < 25,000/µℓ and re-initiated at a reduced dose after resolution (see section 4.2 and 4.8). Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Table 6: The severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Phase 3 Study Multiple Myeloma Study

Pretreatment Platelet Count	**Number of Patients (N=331)***	**Number of Patients with Platelet Count < 10 000/µℓ**	**Number of Patients with Platelet Count 10 000 – 25 000/µℓ**
≥ 75 000/µℓ	**309**	**8 (3 %)**	**36 (12 %)**

> 50 000/µℓ - 75 000/µℓ	**14**	**2 (14 %)**	**11 (79 %)**
≥ 10 000/µℓ - <50 000/µℓ	**7**	**1 (14 %)**	**5 (71 %)**

* Data for one patient was missing at baseline.

Peripheral Neuropathy

BORTIV 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 may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with **BORTIV**. 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 **BORTIV** 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 agent 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. 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

BORTIV treatment is commonly associated with orthostatic/postural hypotension. Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to **BORTIV** or **BORTIV** 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 inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during **BORTIV** treatment.

Pulmonary Disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving **BORTIV**. 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.

Renal Events

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

Hepatic Events

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

Hepatic Impairment

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

Tumour lysis syndrome

Because **BORTIV** is a cytotoxic substance 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 reactions monitored closely and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by **BORTIV** 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. **BORTIV** should be discontinued if severe reactions occur.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Hepatitis B Virus (HBV) reactivation and infection

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

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 as in **BORTIV**. 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 as in **BORTIV**. 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 **BORTIV** if PML is diagnosed.

Any special precaution necessary relating to excipients:

BORTIV contains mannitol (3,5 mg/mL). At doses that exceeds 10 g of mannitol per maximum recommended daily dose **BORTIV** may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

BORTIV 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 **BORTIV** the CYP2D6**,** poor metaboliser phenotype is not expected to affect the overall disposition of **BORTIV**.

Ketoconazole, a potent CYP3A4 inhibitor, showed 35 % increase in mean bortezomib AUC. Therefore, patients should be monitored closely when given **BORTIV** in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir)

Omeprazole, a potent inhibitor of CYP2C19, has no significant effect on the pharmacokinetics of bortezomib.

Concomitant use of bortezomib with rifampicin, a potent CYP3A4 inducer, showed a mean bortezomib AUC reduction of 45 %. Therefore the concomitant use of **BORTIV** with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. Dexamethasone, a weaker CYP3A4 inducer has no significant effect on bortezomib pharmacokinetics.

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

Melphalan-prednisone showed a 17 % increase in mean bortezomib AUC and is not considered clinically relevant. Patients on oral antidiabetic medicines receiving **BORTIV** treatment may require close monitoring of the 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 hypoglycaemic medicines.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

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 **BORTIV** therapy.

Pregnancy

Safety in pregnancy has not been established.

If **BORTIV** is used during pregnancy, or if the patient becomes pregnant while receiving **BORTIV**, the patient needs to be informed of potential for hazards to the foetus. **BORTIV** should be avoided during pregnancy and women are advised to avoid falling pregnant while on treatment with **BORTIV**.

Breastfeeding

Safety in lactation has not been established.

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

receiving **BORTIV**.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of safety profile

Serious adverse reactions uncommonly reported during treatment with **BORTIV** include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

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

b) Tabulated list of adverse reactions

The following undesirable effects included are considered to have at least a possible or probable causal relationship to **BORTIV**.

Infections and infestations:

Frequent: herpes zoster (including disseminated & ophthalmic), pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex.

Less frequent: sepsis (inc. septic shock), bacteraemia, pneumonia pneumococcal, bronchopneumonia, upper

and lower respiratory tract infection, catheter related infection, pleural infection, haemophilus infection, cytomegalovirus infection, influenza, mononucleosis, varicella, urinary tract infection, gastroenteritis, candida infection, fungal infection, post herpetic neuralgia oral candidiasis, blepharitis,

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Less frequent: tumour lysis syndrome, Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign

Blood and the lymphatic system disorders

Frequent: thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia.

Less frequent: pancytopenia, febrile neutropenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy, disseminated intravascular coagulation.

Immune system disorders:

Less frequent: angioedema, hypersensitivity, immune-complex mediated hypersensitivity, potentially immune-complex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis

Endocrine disorders:

Less frequent: inappropriate antidiuretic hormone (ADH) secretion.

Metabolism and nutrition disorders:

Frequent: appetite decreased, dehydration, hypokalaemia, hyperglycaemia.

Less frequent: hyperkalaemia, cachexia, hypercalcaemia, hypocalcaemia, hypernatremia, hyponatraemia, hypoglycaemia, hyperuricaemia, vitamin B12 deficiency, Vitamin B complex deficiency, appetite increased, hypomagnesaemia, hypophosphataemia, Alcohol intolerance.

Psychiatric disorders:

Frequent: confusion, depression, insomnia, anxiety.

Less frequent: agitation, delirium, hallucinations, restlessness, mood swings, mental status changes, sleep disorder, irritability, abnormal dreams.

Nervous system disorders

Frequent: peripheral neuropathy, peripheral sensory neuropathy, paraesthesia, headache, polyneuropathy, peripheral neuropathy aggravated, dizziness, (excluding vertigo), dysgeusia, dysaesthesia, hypoesthesia, tremor.

Less frequent: paraplegia, intracranial haemorrhage, subarachnoid haemorrhage convulsions, peripheral motor neuropathy, syncope, paresis, disturbance in attention, increased activity, ageusia, somnolence, migraine, cognitive disorder, jerky movements, postural dizziness, sciatica, mononeuropathy, speech disorder, restless leg syndrome.

Eye disorders:

Frequent: vision blurred, eye pain.

Less frequent: eye haemorrhage, vision abnormal, keratitis sicca, conjunctivitis, eye discharge, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.

Ear and labyrinth disorders:

Frequent: vertigo.

Less frequent: deafness, tinnitus, hypoacusis, hearing impaired.

Cardiac disorders:

Less frequent: cardiac arrest, cardiogenic shock, myocardial infarction, unstable angina pectoris, development

or exacerbation of congestive heart failure, cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, complete atrioventricular block, tachycardia, sinus tachycardia, supraventricular tachycardia, dysrhythmia, atrial fibrillation, palpitations, new onset of decreased left ventricular ejection fraction.

Vascular disorders:

Frequent: hypotension, orthostatic and postural hypotension, phlebitis, haematoma, hypertension.

Less frequent: cerebral haemorrhage, vasculitis, cerebrovascular accident, pulmonary hypertension, petechiae, ecchymosis, purpura, vein discolouration, vein distended, wound haemorrhage, flushing, hot flushes.

Respiratory, thoracic and mediastinal disorders:

Frequent: dyspnoea, exertional dyspnoea, 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, tongue coated, tongue discolouration, faecal impaction.

Hepato-biliary disorder:

Less frequent: hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia, hepatotoxicity, acute liver failure.

Skin and subcutaneous tissue disorders:

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

Less frequent: vasculitis rash (including leukocytoclastic vasculitis), erythematous rash, photosensitivity reaction, contusion, generalised pruritus, macular rash, popular rash, psoriasis, generalized 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, 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: testicular pain, erectile dysfunction.

General disorders and administration site disorders:

Frequent: fatigue, pyrexia, asthenia, weakness, lethargy, rigors, malaise, influenza like illness, oedema peripheral, 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 phosphate, increased blood creatinine, increased blood urea, increased gamma-glutamyltransferase, increased blood amylase, abnormal liver function test, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, decreased 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, Fall, contusion, Transfusion reaction, Fractures, Rigors, Face injury, Joint injury, Burns, Laceration, Procedural pain, Radiation injuries.

Post marketing experience

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

- Blood and lymphatic system disorders
- Haemolytic anaemia
- Thrombotic microangiopathy (inc thrombocytopenic purpura)

- Cardiac disorders
- Cardiac tamponade
- Eye disorders
- Chalazion
- Blepharitis
- Optic neuropathy
- Gastrointestinal disorders
- Ischaemic colitis
- Infections and infestations
- Herpetic meningoencephalitis
- Immune system disorders
- Angioedema
- Nervous system disorders
- Posterior Reversible Encephalopathy Syndrome
- Guillain-Barré syndrome, demyelinating polyneuropathy
- Respiratory, thoracic and mediastinal disorders
- Pulmonary alveolar haemorrhage
- Skin and subcutaneous tissue disorders
- Toxic epidermal necrolysis
- Stevens-Johnson syndrome
- Decubitus ulcer
- Vascular disorders
- Cerebrovascular accident

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued

monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

Overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported. Overdosage is associated with acute onset of the symptomatic hypotension. It is recommended that in the events 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

Category and class: A 26 Cytostatic agents

Mechanism of action

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory protein, 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 tumorigenesis, 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

Absorption

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mℓ respectively after the first dose. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mℓ for the 1,0 mg/m^2 dose and 89 to 120 ng/mℓ for the 1,3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours.

Distribution

The mean distribution volume of bortezomib was variable and ranged from 1 659 litres to 3 294 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.

Biotranformation

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 206 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 drug.

Elimination

The mean elimination half-life (t1/2) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively, and ranged from 15 to 32 L/h and 18 to 32 L/h following subsequent doses for doses of 1,0 mg/m2 and 1,3 mg/m^2, respectively.

Special populations

Age, Gender and Race

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 - 16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (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-normalised clearance of bortezomib in paediatric patients was similar to that observed in adults.

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

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in cancer patients 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-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients

should be monitored closely (see table 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/1,73 m^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 bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups (see section 4.2).

Environmental Risk Assessment:

Bortezomib is a well established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites is expected to be very limited. The use of **BORTIV** is not considered warranting any environmental concerns or requiring any special product labelling.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (25 mg/mL),

Sodium chloride,

Sodium Hydroxide,

Hydrochloric acid Concentrated,

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 2°C - 8°C, in a dry place, well closed in original vial, protected from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

Keep the vial in the carton.

Discard unused portion after dosing

6.5 Nature and contents of container

BORTIV 1 mg/0.4 mL

Type 1 glass 10 mL-vial with a Igloo GCB Grey EPP rubber stopper and Orange colour flip off seal contacting 2,5 mg/mL of Bortezomib

BORTIV 2.5 mg/1 mL

Type 1 glass 10 mL-vial with a Igloo GCB Grey EPP rubber stopper and White colour flip off seal contacting 2,5 mg/mL of Bortezomib

BORTIV 3.5 mg/1.4 mL

Type 1 glass 10 mL-vial with a Igloo GCB Grey EPP rubber stopper and Yellow matte top colour flip off seal contacting 2,5 mg/mL of Bortezomib

Each vial placed into a carton box. Each pack contains 1 single-use vial together with a package insert.

6.6 Special precautions for disposal and other handling

BORTIV IS FOR SINGLE USE ONLY.

BORTIV is a cytotoxic medicine. 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 BORTIV SINCE NO PRESERVATIVE IS PRESENT

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall corporate campus,

Building no. 2, first floor,

74 waterfall drive,

Midrand 2066.

Tel.: 0126441220

8 REGISTRATION NUMBER(S)

BORTIV 1 mg/0.4 ml: 57/26/0412.409

BORTIV 2.5 mg/ml: 57/260413.410

BORTIV 3.5 mg/1.4 ml: 57/26/0414.411

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

22 JULY 2025

10 DATE OF REVISION OF THE TEXT

N/A