PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BORTURAS 3,5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For SC use: After reconstitution, 1 mL of solution for subcutaneous injection contains 2,5 mg bortezomib.

For IV use: After reconstitution, 1 mL of solution for intravenous injection contains 1 mg bortezomib.

Excipients with known effects

Contains mannitol (35 mg per vial).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white to off white colour, lyophilised powder or plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BORTURAS is indicated as:

- Primary treatment of multiple myeloma in combination with melphalan and prednisone.
- Monotherapy for the treatment of patients with multiple myeloma who have received at least one prior therapy and who have progressive disease.

- Treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.

4.2 Posology and method of administration

Posology

BORTURAS 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 of 2,5 mg/mL.

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

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

See section 6.6 for reconstitution instructions.

Monotherapy

Recommended dosage

The recommended starting dose of BORTURAS 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 BORTURAS.

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

There is limited data concerning re-treatment with BORTURAS.

Recommended dosage adjustments during treatment and re-initiation of treatment

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

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

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

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

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue BORTURAS

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

Special populations

Paediatric patients

BORTURAS 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 BORTURAS are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BORTURAS are not necessary for patients with renal insufficiency. Since dialysis may reduce BORTURAS concentrations, BORTURAS 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 BORTURAS dose. Patients with moderate or severe hepatic impairment should be started on BORTURAS at a reduced dose of 0,7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see Table 2).

Table 2: Recommended starting dose modification for BORTURAS 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 BORTURAS 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	

* Based on NCI organ dysfunction working group classification for categorising hepatic impairment (mild, moderate, severe).

SGOT = serum glutamic oxaloacetic transaminase

AST = aspartate aminotransferase

ULN = upper limit of the normal range.

Combination therapy

Recommended dosage

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

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

Twice weekly BORTURAS (cycles 1 – 4)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
BORTURAS (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 BORTURAS (cycles 5 – 9)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
BORTURAS (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

m = melphalan, p = prednisone

Dose management guidelines for combination therapy

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

Prior to initiating a new cycle of therapy:

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

Table 4: Dose modifications during subsequent cycles.

Toxicity	Dose modification or delay
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia, 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 $\leq 30 \times 10^9$/L or ANC ≤ 0,75 x 10^9/L on a BORTURAS dosing day (other than day 1).	BORTURAS dose should be withheld.
• If several BORTURAS doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration).	BORTURAS 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	BORTURAS therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BORTURAS 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 BORTURAS related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTURAS as outlined in Table 1.

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

Method of administration

Administration precautions

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

DO NOT ADMINISTER BORTURAS INTRATHECALLY.

Intravenous (IV) 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 BORTURAS.

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

4.3 Contraindications

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

experienced in the use of chemotherapeutic medicines.

When BORTURAS is given in combination with other medicines, the Professional Information (PI) of these other medicines must be consulted prior to initiation of treatment with BORTURAS. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib, as in BORTURAS. BORTURAS is for intravenous or subcutaneous use. BORTURAS should not be administered intrathecally.

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation occur very frequently with BORTURAS treatment. 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 and therefore patients who experience constipation should be closely monitored (see section 4.8).

Haematological toxicity

BORTURAS treatment is frequently associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is an uncommon undesirable effect. In studies in patients with relapsed multiple myeloma treated with bortezomib and in patients with previously untreated MCL treated with bortezomib, as in BORTURAS, in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP), one of the most common haematologic toxicity was transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at day 11 of each cycle of bortezomib 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 in the single-treatment multiple myeloma studies and 50 % in the MCL study. Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75 000/µL, 90 % of 21 patients had a count ≤ 25 000/µL during the study, including 14 % < 10 000/µL; in contrast, with a baseline platelet count > 75 000/µL, only 14 % of 309 patients had a count ≤ 25 000/µL during clinical studies.

During clinical studies in patients with MCL, there was a higher incidence of Grade ≥ 3 thrombocytopenia in the group treated with bortezomib (BR-CAP) as compared to the non-bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events, as well as Grade 3 and higher bleeding events.
In the BR-CAP group, 22,5 % of patients received platelet transfusions compared to 2,9 % of patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage have been reported in association with BORTURAS treatment.
Therefore, platelet counts should be monitored prior to each dose of BORTURAS. Therapy should be withheld when the platelet count is < 25 000/µL or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30 000/µL (see section 4.2). Therapy should be re-initiated at a reduced dose after resolution. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with BORTURAS. Platelet transfusion should be considered when

clinically appropriate (see section 4.2).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTURAS.
In clinical studies in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with BORTURAS + Melphalan + Prednisone compared with Melphalan + Prednisone.

Hepatitis B virus (HBV) reactivation and infection

When rituximab is used in combination with BORTURAS, 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 BORTURAS. 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. 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 BORTURAS if PML is diagnosed.

Peripheral neuropathy

Treatment with bortezomib, as in BORTURAS is frequently associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with BORTURAS. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

In clinical studies comparing bortezomib administered intravenously versus subcutaneously, the incidence of grade ≥ 2 peripheral neuropathy events were 24 % for the subcutaneous injection group and 41 % for the intravenous injection group. Grade ≥ 3 peripheral neuropathy occurred in 6 % of patients in the subcutaneous treatment group, compared with 16 % in the intravenous treatment group. Therefore, patients with pre-existing peripheral neuropathy or those at high risk for peripheral neuropathy may benefit from starting bortezomib subcutaneously.
Patients experiencing new or worsening peripheral neuropathy may require a change in the dose schedule of BORTURAS (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 during a

clinical study and 71 % of patients with grade 3 or 4 peripheral neuropathy.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving BORTURAS in combination with medicines known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

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 MCL.

Seizures

Seizures have less frequently 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

Bortezomib, as in BORTURAS treatment is frequently associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on bortezomib (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with bortezomib. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of

orthostatic/postural hypotension may include adjustment of antihypertensive medicines, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior reversible encephalopathy syndrome (PRES)

There have been reports of PRES in patients receiving bortezomib. PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably magnetic resonance imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, BORTURAS should be discontinued. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.

Heart failure

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

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 BORTURAS treatment.

Electrocardiogram investigations

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

Pulmonary disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS)

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

In the event of new or worsening pulmonary symptoms (e.g. cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately.

In clinical trials, two patients (out of 2) given high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy, and the study was terminated. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Renal impairment

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

Hepatic impairment

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

Hepatic reactions

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

Tumour lysis syndrome

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

Amyloidosis

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

Concomitant medicines

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

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

Potentially immunocomplex-mediated reactions

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

Patients with mantle cell lymphoma

Safety data for patients with mantle cell lymphoma were evaluated in patients treated with bortezomib at the recommended dose of 1,3 mg/m^2.

The safety profile of bortezomib in these patients was similar to that observed in patients with multiple

myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, 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 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 BORTURAS.

4.5 Interaction with other medicines and other forms of interaction

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

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35 % ($CI_{90\ \%}$ (1,032 to 1,772)) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In an interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the

pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.

An interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St John's wort) is not recommended, as efficacy may be reduced.
In the same interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.

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

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

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemic medicines. Patients on oral antidiabetic medicines receiving BORTURAS may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines.
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 potential should use effective contraceptive measures during and for 3 months following BORTURAS treatment.

Pregnancy

Safety in pregnancy has not been established. The teratogenic potential of bortezomib has not been fully investigated.

If BORTURAS is used during pregnancy, alone or in combination with other medicines or if the patient becomes pregnant while receiving BORTURAS, the patient needs to be informed of potential hazards to the foetus.

Breastfeeding

Safety in lactation has not been established.

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

Fertility

Fertility studies have not been conducted.

4.7 Effects on ability to drive and use machines

BORTURAS may have a moderate influence on the ability to drive a vehicle and use machines. BORTURAS may cause side effects, such as fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Caution is advised before driving a vehicle or operating machinery until the effects of BORTURAS are known. Patients should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

Table 5: Adverse reactions in patients treated with bortezomib and all post-marketing adverse reactions regardless of indication[#].

System organ class	Incidence	Adverse reaction
Infections and infestations	Frequent	herpes zoster (including disseminated and ophthalmic), pneumonia*, herpes simplex*, fungal infection*
	Less frequent	infection*, bacterial infections*, viral infections*, sepsis (including septic shock)*, bronchopneumonia, herpes virus infection*, meningoencephalitis herpetic[#], bacteraemia (including staphylococcal), hordeolum, influenza, cellulitis, device related infection, skin infection*, ear infection*, staphylococcal infection, tooth infection*, meningitis (including bacterial), Epstein-Barr

System organ class	Incidence	Adverse reaction
		virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign*
Blood and lymphatic system disorders	Frequent	thrombocytopenia*, neutropenia*, anaemia*, leukopenia*, lymphopenia*
	Less frequent	pancytopenia*, febrile neutropenia, coagulopathy*, leucocytosis*, lymphadenopathy, haemolytic anaemia#, disseminated intravascular coagulation, thrombocytosis*, hyperviscosity syndrome, platelet disorder NOS, thrombotic microangiopathy (including thrombocytopenic purpura) #, blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration
Immune system disorders	Less frequent	angioedema#, hypersensitivity*, anaphylactic shock, amyloidosis, type III immune complex mediated reaction
Endocrine disorders	Less frequent	Cushing's syndrome*, hyperthyroidism*, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutrition disorders	Frequent	decreased appetite, dehydration, hypokalaemia*, hyponatraemia*, abnormal blood glucose*, hypocalcaemia*, enzyme abnormality*, anorexia

System organ class	Incidence	Adverse reaction
	Less frequent	tumour lysis syndrome, failure to thrive*, hypomagnesaemia*, hypophosphatemia*, hyperkalaemia*, hypercalcaemia*, hypernatremia*, abnormal uric acid*, diabetes mellitus*, fluid retention, hypermagnesemia*, acidosis, electrolyte imbalance*, fluid overload, hypochloraemia*, hypovolaemia, hyperchloremia*, hyperphosphatemia*, metabolic disorder, vitamin B complex deficiency, vitamin B12 deficiency, gout, increased appetite, alcohol intolerance
Psychiatric disorders	Frequent	mood disorders and disturbances*, anxiety disorder*, sleep disorders and disturbances*, insomnia
	Less frequent	mental disorder*, hallucination*, psychotic disorder*, confusion*, restlessness, suicidal ideation*, adjustment disorder, delirium, decreased libido
Nervous system disorders	Frequent	neuropathies*, peripheral sensory neuropathy, dysesthesia*, neuralgia*, motor neuropathy*, loss of consciousness (including syncope), dizziness*, dysgeusia*, lethargy, headache*, paraesthesia
	Less frequent	tremor, peripheral sensorimotor neuropathy, dyskinesia*, cerebellar coordination and balance disturbances*, memory loss (excluding dementia)*, encephalopathy*, posterior reversible encephalopathy syndrome#, neurotoxicity, seizure disorders*, post herpetic neuralgia, speech disorder*, restless legs syndrome, migraine, sciatica, disturbance in attention,

System organ class	Incidence	Adverse reaction
		abnormal reflexes*, parosmia, cerebral haemorrhage*, haemorrhage intracranial (including subarachnoid)*, brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, autonomic neuropathy, cranial palsy*, paralysis*, paresis*, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder NOS, motor dysfunction, nervous system disorder NOS, radiculitis, drooling, hypotonia, Guillain-Barré syndrome#, demyelinating polyneuropathy#
Eye disorders	Frequent	eye swelling*, abnormal vision*, conjunctivitis*
	Less frequent	eye haemorrhage*, eyelid infection*, chalazion#, blepharitis#, eye inflammation*, diplopia, dry eye*, eye irritation*, eye pain, lacrimation increased, eye discharge, corneal lesion*, exophthalmos, retinitis, scotoma, eye disorder (including eyelid) NOS, dacryoadenitis acquired, photophobia, photopsia, optic neuropathy#, different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Frequent	vertigo*
	Less frequent	dysacusis (including tinnitus)*, hearing impaired (up to and including deafness), ear discomfort*, ear haemorrhage, vestibular neuronitis, ear disorder NOS

System organ class	Incidence	Adverse reaction
Cardiac disorders	Less frequent	cardiac tamponade[#], cardio-pulmonary arrest*, cardiac fibrillation (including atrial), cardiac failure (including left and right ventricular)*, dysrhythmia*, tachycardia*, palpitations, angina pectoris, pericarditis (including pericardial effusion)*, cardiomyopathy*, ventricular dysfunction*, bradycardia, atrial flutter, myocardial infarction*, atrioventricular block*, cardiovascular disorder (including cardiogenic shock), torsades de pointes, unstable angina, cardiac valve disorders*, coronary artery insufficiency, sinus arrest
Vascular disorders	Frequent	hypotension*, orthostatic hypotension, hypertension*
	Less frequent	cerebrovascular incident[#], deep vein thrombosis*, haemorrhage*, thrombophlebitis (including superficial), circulatory collapse (including hypovolaemic shock), phlebitis, flushing*, haematoma (including perirenal)*, poor peripheral circulation*, vasculitis, hyperaemia (including ocular)*, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders	Frequent	dyspnoea*, epistaxis, upper/lower respiratory tract infection*, cough*
	Less frequent	pulmonary embolism, pleural effusion, pulmonary oedema (including acute), pulmonary alveolar haemorrhage[#], bronchospasm, chronic obstructive pulmonary disease*, hypoxaemia*, respiratory tract

System organ class	Incidence	Adverse reaction
		congestion*, hypoxia, pleurisy*, hiccups, rhinorrhoea, dysphonia, wheezing, respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, haemoptysis, hyperventilation, orthopnoea, pneumonitis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial disorder*, hypocapnia*, interstitial lung disease, lung infiltration, throat tightness, dry throat, increased upper airway secretion, throat irritation, upper-airway cough syndrome
Gastrointestinal disorders	Frequent	nausea and vomiting symptoms*, diarrhoea*, constipation, gastrointestinal haemorrhage (including mucosal)*, dyspepsia, stomatitis*, abdominal distension, oropharyngeal pain*, abdominal pain (including upper abdominal pain, gastrointestinal and splenic pain)*, oral disorder*, flatulence
	Less frequent	pancreatitis (including chronic)*, haematemesis, lip swelling*, gastrointestinal obstruction (including small intestinal obstruction, ileus)*, abdominal discomfort, oral ulceration*, enteritis*, gastritis*, gingival bleeding, gastroesophageal reflux disease*, colitis (including clostridium difficile)*, colitis ischaemic#, gastrointestinal inflammation*, dysphagia, irritable bowel syndrome, gastrointestinal disorder NOS, tongue coated, gastrointestinal motility disorder*, salivary gland

System organ class	Incidence	Adverse reaction
		disorder*, pancreatitis acute, peritonitis*, tongue oedema*, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma*, gastrointestinal ulceration and perforation*, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering*, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces
Hepatobiliary disorders	Frequent	hepatic enzyme abnormality*
	Less frequent	hepatotoxicity (including liver disorder), hepatitis*, cholestasis, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis
Skin and subcutaneous tissue disorders	Frequent	rash*, pruritus*, erythema, dry skin
	Less frequent	erythema multiforme, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis#, Stevens-Johnson syndrome#, dermatitis*, hair disorder*, petechiae, ecchymosis, skin lesion, purpura, skin mass*, psoriasis, hyperhidrosis, night sweats, decubitus ulcer#, acne*, blister*, pigmentation disorder*, skin reaction, Jessner's lymphocytic infiltration, palmar-plantar erythrodysesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction,

System organ class	Incidence	Adverse reaction
		seborrhoea, cold sweat, skin disorder NOS, erythrosis, skin ulcer, nail disorder
Musculoskeletal and connective tissue disorders	Frequent	musculoskeletal pain*, muscle spasms*, pain in extremity, muscular weakness
	Less frequent	muscle twitching, joint swelling, arthritis*, joint stiffness, myopathies*, sensation of heaviness, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, pain in jaw, bone disorder, musculoskeletal and connective tissue infections and inflammations*, synovial cyst
Renal and urinary disorders	Frequent	renal impairment*
	Less frequent	renal failure acute, renal failure chronic*, urinary tract infection*, urinary tract signs and symptoms*, haematuria*, urinary retention, micturition disorder*, proteinuria, azotaemia, oliguria*, pollakiuria, bladder irritation
Reproductive system and breast disorders	Less frequent	vaginal haemorrhage, genital pain*, erectile dysfunction, testicular disorder*, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders	Less frequent	aplasia, gastrointestinal malformation, ichthyosis

System organ class	Incidence	Adverse reaction
General disorders and administration site conditions	Frequent	pyrexia*, fatigue, asthenia, oedema (including peripheral), chills, pain*, malaise*
	Uncommon	general physical health deterioration*, face oedema*, injection site reaction*, mucosal disorder*, chest pain, gait disturbance, feeling cold, extravasation*, catheter related complication*, change in thirst*, chest discomfort, feeling of body temperature change*, injection site pain*, death (including sudden), multi-organ failure, injection site haemorrhage*, hernia (including hiatus)*, impaired healing*, inflammation, injection site phlebitis*, tenderness, ulcer, irritability, non-cardiac chest pain, catheter site pain, sensation of foreign body
Investigations	Frequent	weight decreased
	Less frequent	hyperbilirubinemia*, protein analyses abnormal*, weight increased, abnormal blood test *, increased C-reactive protein, abnormal blood gases*, electrocardiogram abnormalities (including QT prolongation)*, abnormal international normalised ratio *, decreased gastric pH, increased platelet aggregation, increased troponin I, virus identification and serology*, abnormal urine analysis*
Injury, poisoning and procedural complications	Less frequent	fall, contusion, transfusion reaction, fractures*, rigors*, face injury, joint injury*, burns, laceration, procedural pain, radiation injuries*

System organ class	Incidence	Adverse reaction
Surgical and medical procedures	Less frequent	macrophage activation

NOS = not otherwise specified

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BORTURAS is important. It allows continued monitoring of the benefit/risk balance of BORTURAS. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform(who-umc-org) found on SAHPRA website.

4.9 Overdose

In patients, overdose with more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. One case of overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported.

Management

There is no known specific antidote for BORTURAS overdose. It is recommended that in the event of overdosage, patients should undergo careful haemodynamic monitoring, and hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents.

ATC code: L01XX32.

Mechanism of action

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

Bortezomib is highly selective for the proteasome. At 10 μM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1 500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a half-life of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including

multiple myeloma.

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

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to eleven patients with multiple myeloma and creatinine clearance values greater than 50 mL/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1,0 mg/m^2 dose and 89 to 120 ng/mL for the 1,3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1,3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administrations. The C_{max} after subcutaneous administration (20,4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0,99 and 90 % confidence intervals were 80,18 % – 122,80 %.

Distribution

The mean distribution volume (V_d) of bortezomib ranged from 1 659 L to 3 294 L following single- or repeated-dose intravenous administration of 1,0 mg/m^2 or 1,3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. Over a bortezomib concentration range of 0,01 to 1,0 µg/mL, the *in vitro* protein binding averaged 82,9 % in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration dependent.

Biotransformation

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination

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

The pathway of elimination of bortezomib have not been characterised in humans.

Pharmacokinetics in special populations

Hepatic impairment

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

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib area under the curve (AUC). However, the dose-normalised mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored (see section 4.2).

Renal impairment

A pharmacokinetic study was conducted in patients with various degrees of renal impairment who

were classified according to their creatinine clearance values (CrCL) into the following groups: normal (CrCL ≥ 60 mL/min/1,73 m^2), mild (CrCL = 40 – 59 mL/min/1,73 m^2), moderate (CrCL = 20 – 39 mL/min/1,73 m^2), and severe (CrCL < 20 mL/min/1,73 m^2). A group of dialysis patients who were dosed after dialysis was also included in the study. Patients were administered intravenous doses of 0,7 to 1,3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

Age

The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 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 pediatric patients was similar to that observed in adults.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421).

6.2 Incompatibilities

BORTURAS must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years.

Reconstituted solution

The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25 °C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicine should not exceed 8 hours prior to administration.

6.4 Special precautions for storage

Store at or below 25 °C.

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

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

6.5 Nature and contents of container

10 mL, 20 mm flint flat bottom tubular USP type-I glass vials with 20 mm dark grey bromobutyl rubber stoppers (RFS) and 20 mm aluminium seal with light blue colour flip-off cap.

One vial is packed in an outer carton.

6.6 Special precautions for disposal and other handling

General precautions

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

Aseptic technique must be strictly observed throughout the handling of BORTURAS, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of BORTURAS. BORTURAS is

for intravenous or subcutaneous use.

BORTURAS should not be administered intrathecally.

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.

Instructions for reconstitution

BORTURAS must be reconstitued by a health care provider.

Intravenous injection

Each 10 mL vial of BORTURAS must be carefully reconstituted with 3,5 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each mL solution contains 1 mg bortezomib. 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 solution must be discarded.

Subcutaneous injection

Each 10 mL vial of BORTURAS must be carefully reconstituted with 1,4 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each mL solution contains 2,5 mg bortezomib. 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 solution must be discarded.

Disposal

BORTURAS is for single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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Johannesburg

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8. REGISTRATION NUMBER

56/26/0790

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 August 2025

10. DATE OF REVISION OF THE TEXT

To follow