PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

BORTEZOMIB ADCO 3,5 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3,5 mg bortezomib.

For intravenous or subcutaneous use.

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

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

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

White to off-white, lyophilized cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bortezomib Adco is indicated in adults 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;

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- 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

Bortezomib Adco 3,5 mg powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg/ml (as a 3 - 5 second bolus injection) or
- subcutaneous administration at a concentration 2,5 mg/ml.

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

Bortezomib Adco **should not** be given by other routes. Intrathecal administration has resulted in death.

Monotherapy

The recommended starting dose of Bortezomib Adco is 1,3 mg/m² 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 Bortezomib Adco.

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

There is limited data concerning re-treatment with Bortezomib Adco.

Recommended dosage adjustments during treatment and re-initiation of treatment

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Bortezomib Adco 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, Bortezomib Adco treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m² reduced to 1,0 mg/m²; 1,0 mg/m² reduced to 0,7 mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of Bortezomib Adco must be considered.

Patients who experience Bortezomib Adco 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 Bortezomib Adco only after careful risk/benefit assessment.

Table 1: Recommended dose modifications for Bortezomib Adco 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/m²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold Bortezomib Adco treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate Bortezomib Adco treatment and reduce dose to 0,7 mg/m² and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue Bortezomib Adco

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Combination Therapy

Bortezomib Adco (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2. In Cycles 1 - 4, Bortezomib Adco is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 - 9, Bortezomib Adco is administered once weekly (days 1, 8, 22 and 29).

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

Twice Weekly Bortezomib (Cycles 1 – 4)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
Bz (1,3 mg/m²)	Day 1 Day 4	Day 8 Day 11	Rest period	Day 22 Day 25	Day 29 Day 32	Rest period
M (9 mg/m²) P (60 mg/m²)	Day 1 Day 2 Day 3 Day 4	-- --	Rest period	-- --	-- --	Rest period

Once Weekly Bortezomib (Cycles 5 – 9)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
Bz (1,3 mg/m²)	Day 1 -- -- --	Day 8	Rest period	Day 22	Day 29	Rest period
M (9 mg/m²) P (60 mg/m²)	Day 1 Day 2 Day 3 Day 4	--	Rest period	--	--	Rest period

Bz = BORTEZOMIB; M = melphalan; P=prednisone

Dose Management Guidelines for Combination Therapy

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

Prior to initiating a new cycle of therapy:

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

Table 3: Dose modifications during subsequent cycles:

Toxicity	***Dose modification or delay***
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.
• If platelet count ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a Bortezomib Adco dosing day (other than day 1)	Bortezomib Adco dose should be withheld
• If several Bortezomib Adco doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib Adco dose should be reduced by 1 dose level (from 1,3 mg/m² to 1 mg/m², or from 1 mg/m² to 0,7 mg/m²)
Grade ≥ 3 non-haematological toxicities	Bortezomib Adco therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, Bortezomib Adco may be reinitiated with one dose level reduction (from 1,3 mg/m²

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	to 1 mg/m², or from 1 mg/m² to 0,7 mg/m²). For Bortezomib Adco-related neuropathic pain and/or peripheral neuropathy, hold and/or modify Bortezomib Adco as outlined in Table 1.

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

Special populations

Elderly patients

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

Renal Impairment

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

Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended Bortezomib Adco dose. Patients with moderate or severe hepatic impairment should be started on Bortezomib Adco at a reduced dose of 0,7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² may be considered based on patient tolerance (see Table 4).

Table 4: Recommended Starting Dose Modification for Bortezomib Adco in Patients with Hepatic Impairment

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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 Bortezomib Adco to 0,7 mg/m² in the first cycle. Consider dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

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

Paediatric population

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

Method of administration

Precaution to be taken before manipulating or administering the product Refer to section 6.6 Special precautions for disposal and other handling.

Inadvertent intrathecal administration of Bortezomib Adco may be fatal.

DO NOT ADMINISTER Bortezomib Adco INTRATHECALLY.

Bortezomib Adco

Intravenous injection:

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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 Bortezomib Adco.

Subcutaneous injection:

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

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

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to boron, or to any of the excipients of Bortezomib Adco listed in section 6.1.

Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use

Bortezomib Adco should be initiated and administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicines.

Inadvertent intrathecal administration of Bortezomib Adco may be fatal.

Bortezomib Adco 3,5 mg is for IV or SC use.

DO NOT ADMINISTER Bortezomib Adco INTRATHECALLY.

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Women should not become pregnant during treatment. Women of childbearing potential must use effective contraception to avoid pregnancy while they are receiving Bortezomib Adco. The recommended duration of contraception in female patients of childbearing potential is until the end of the relevant systemic exposure to Bortezomib Adco including potential metabolites (i.e.: five half-life's after the last dose) plus 6 months. On this basis, female patients of childbearing potential should be advised to use effective contraception during treatment with Bortezomib Adco and for at least 8 months after the final dose.

Male patients should be advised not to father a child during treatment and should be advised on the use of effective contraception to avoid conception. The recommended duration of contraception in male patients is until the end of the relevant systemic exposure to Bortezomib Adco including potential metabolites (i.e.: five half-life's after the last dose) plus 3 months. On this basis male patients should be advised on the use of effective contraception during treatment with Bortezomib Adco and for at least 5 months after the final dose (see section 4.6). Male patients should also be counselled to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Bortezomib Adco.

Herpes Zoster Virus Reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with Bortezomib Adco.

Patients with mantle cell lymphoma:

Safety profile of Bortezomib Adco between patients with multiple myeloma and mantle cell lymphoma is similar.

Patients with mantle cell lymphoma may experience peripheral neuropathy, rash and puritis whereas patients with multiple myeloma may experience thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia.

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Safety profile is similar between treatment with Bortezomib Adco in monotherapy and Bortezomib Adco in combination with melphalan and prednisolone.

Laboratory Tests

Full blood counts (FBC) including platelet counts should be frequently monitored throughout treatment with Bortezomib Adco.

Gastrointestinal toxicity

Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with Bortezomib Adco 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

Bortezomib Adco 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. The cyclical pattern of platelet decrease and recovery remains consistent with no evidence of cumulative thrombocytopenia. Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia may occur. In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count. Platelet counts should be monitored prior to each dose of Bortezomib Adco. Therapy should be held when the platelet count is < 25 000/µl and re-initiated at a reduced dose after resolution (see section 4.8). Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors

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may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Peripheral Neuropathy

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

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with Bortezomib Adco. 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, hypaesthesia, paraesthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of Bortezomib Adco 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 has been reported in patients with ≥ Grade 2 peripheral neuropathy and patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment.

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

Bortezomib Adco 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 Bortezomib Adco or Bortezomib Adco may aggravate an underlying condition such as diabetic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension is symptomatic and may include adjustment of antihypertensive medicines, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Cardiac Disorders

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

There have been cases of QT-interval prolongation; causality has not been established.

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

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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 Bortezomib Adco. 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, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of Bortezomib Adco. There is limited re-challenge information in these patients.

Hepatic Impairment

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

Tumour lysis syndrome

Because Bortezomib Adco is a cytotoxic medicine and can rapidly kill malignant plasma cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of Tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure,

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dysrhythmias and syncope. These patients should be monitored closely and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by Bortezomib Adco 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. Bortezomib Adco should be discontinued if severe reactions occur.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving Bortezomib Adco. 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 Bortezomib Adco. The safety of reinitiating Bortezomib Adco therapy in patients previously experiencing PRES is not known.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with Bortezomib Adco, 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 Bortezomib Adco. Antiviral prophylaxis should be considered.

Progressive multifocal leukoencephalopathy (PML)

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Cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with Bortezomib Adco. 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 Adco. 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 Bortezomib Adco if PML is diagnosed.

Concomitant medicines

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

4.5 Interactions with other medicines and other forms of interaction

Bortezomib Adco 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 Adco the CYP2D6, poor metaboliser phenotype is not expected to affect the overall disposition of Bortezomib Adco.

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

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

The concomitant use of Bortezomib Adco with strong CYP3A4 inducers is not recommended, as efficacy of Bortezomib Adco may be reduced. Examples of CYP3A4 inducers are rifampicin,

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carbamazepine, phenytoin, phenobarbitone and St. John's Wort. Dexamethasone, a weak CYP3A4 inducer has no significant effect on Bortezomib Adco efficacy.

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. Hypoglycaemia and hyperglycaemia may be experienced in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving Bortezomib Adco treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication. Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics.

Paediatric population

Not for paediatric use, see section 4.2

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception to avoid pregnancy while they are receiving Bortezomib Adco, and for at least 8 months following completion of treatment (i.e.: after the final dose).

Pregnancy

Bortezomib Adco is contraindicated in pregnancy.

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

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Breastfeeding

Safety in lactation has not been established. It is not known whether Bortezomib Adco is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from mothers on Bortezomib Adco, women should not breastfeed their infants while receiving Bortezomib Adco.

Fertility

Male fertility

Bortezomib Adco can have genotoxic effects. Therefore, male patients should not father a child during and up to 5 months following completion of treatment (i.e.: after the final dose). Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Bortezomib Adco.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

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

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

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b. Tabulated summary of adverse reactions

Infection and Infestations	
Frequent	Herpes zoster (includes disseminated and ophthalmic), pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex, fungal infection
Less frequent	Infection, bacterial infections, viral infections, sepsis (including septic shock), pneumonia (especially pneumococcal), bronchopneumonia, herpes virus infection, meningoencephalitis herpetic, bacteraemia (including staphylococcal), hordeolum, influenza, cellulitis, device related infection, skin infection, ear infection, staphylococcal infection, tooth infection, upper and lower respiratory tract infection, catheter related infection, pleural infection, haemophilus infection, cytomegalovirus infection, infectious mononucleosis, varicella, urinary tract infection, gastroenteritis, candida infection, fungal infection, post herpetic neuralgia, oral candidiasis, blepharitis
Neoplasms benign, malignant and unspecified (incl 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, leukocytosis, 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	

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Less frequent	Angioedema, hypersensitivity, polyarthritis with rash and proliferative glomerulonephritis, anaphylactic shock, amyloidosis, type III immune complex mediated reaction, potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction
Endocrine disorders	
Less frequent	Cushing's syndrome, hyperthyroidism, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutritional disorders	
Frequent	Decreased appetite, dehydration, hypokalaemia, hyponatraemia, blood glucose abnormal, hypocalcaemia, enzyme abnormality
Less frequent	Tumour lysis syndrome (see section 4.4), failure to thrive, hypomagnesaemia, hypophosphataemia, hyperkalaemia, hypercalcaemia, hypernatraemia, uric acid abnormal, diabetes mellitus, fluid retention, hypermagnesaemia, acidosis, electrolyte imbalance, fluid overload, hypochloraemia, hypovolaemia, hyperchloraemia, hyperphosphataemia, metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, gout, increased appetite, alcohol intolerance
Psychiatric disorders	
Frequent	Mood disorders and disturbances, anxiety disorder, sleep disorders and disturbances
Less frequent	Mental disorder, hallucination, psychotic disorder, confusion, restlessness, suicidal ideation, adjustment disorder, delirium, libido decreased, agitation, irritability, abnormal dreams
Nervous system disorders	
Frequent	Neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, motor neuropathy, loss of consciousness (including syncope), dizziness, dysgeusia, lethargy, headache, tremor

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Less frequent	Peripheral sensorimotor neuropathy, dyskinesia, cerebellar coordination and balance disturbances, memory loss (excluding dementia), encephalopathy, posterior reversible leukoencephalopathy syndrome, neurotoxicity, seizure disorders, post herpetic neuralgia, speech disorder, restless legs syndrome, migraine, sciatica, disturbance in attention, reflexes abnormal, 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
Eye disorders	
Frequent	Eye swelling, vision abnormal, 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, hypoacusis
Cardiac disorders	

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Less frequent	Cardiac tamponade, cardio-pulmonary arrest, cardiac fibrillation (including atrial), cardiac failure (including left and right ventricular), arrhythmia, tachycardia, palpitations, angina pectoris, pericarditis (including pericardial effusion), cardiomyopathy, ventricular dysfunction, bradycardia atrial flutter, myocardial infarction, atrioventricular block, cardiovascular disorder (including cardiogenic shock), torsade de pointes, angina unstable, cardiac valve disorders, coronary artery insufficiency, sinus arrest, new onset of decreased left ventricular ejection fraction
Vascular disorders	
Frequent	Hypotension, orthostatic hypotension, hypertension, haematoma, phlebitis
Less frequent	Cerebral haemorrhage, vasculitis, cerebrovascular accident, deep vein thrombosis, pulmonary hypertension, petechiae, ecchymosis, pupura, haemorrhage, thrombophlebitis (including superficial), circulatory collapse (including hypovolaemic shock), flushing, poor peripheral circulation, vasculitis, hyperaemia (including ocular), peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders	
Frequent	Dyspnoea and exertional 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

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	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, chest wall pain, hiccups
Gastrointestinal disorders (See section 4.4)	
Frequent	Nausea and vomiting symptoms, diarrhoea, constipation, gastrointestinal haemorrhage (including mucosal), dyspepsia, stomatitis, abdominal distension, oropharyngeal pain, abdominal pain (including gastrointestinal and splenic pain), oral disorder, flatulence, oral ulceration, loose stools
Less frequent	Pancreatitis (including chronic), haematemesis, lip swelling, gastrointestinal obstruction (including small intestinal obstruction, ileus), abdominal discomfort, enteritis, gastritis, gingival bleeding, gastro-oesophageal reflux disease, colitis (including clostridium difficile), colitis ischaemic, gastrointestinal inflammation, dysphagia, irritable bowel syndrome, gastrointestinal disorder NOS, tongue coated, gastrointestinal motility disorder, salivary gland disorder, pancreatitis acute, peritonitis, tongue oedema, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma, gastrointestinal ulceration and perforation, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces, retching, spleen pain, oral mucosal petechiae, salivary hypersecretion

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Hepatobiliary disorders (See section 4.4)	
Frequent	Hepatic enzyme abnormality
Less frequent	Hepatotoxicity (including liver disorder), hepatitis, cholestasis, hepatic failure, hepatomegaly, budd-chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis, hypoproteinaemia, hyperibilirubinaemia
Skin and subcutaneous tissue disorders	
Frequent	Rash, pruritus, erythema, dry skin, periorbial oedema, eczema, urticaria hyperhydrosis
Less frequent	Erythema multiforme, acute febrile neutrophilic, dermatosis, toxic skin eruption, toxic epidermal necrolysis, stevens-johnson syndrome, dermatitis, hair disorder, petechiae, ecchymosis, skin lesion, purpura, skin mass, psoriasis, night sweats, decubitus ulcer, acne, blister, pigmentation disorder, skin reaction, jessner's lymphocytic infiltration, palmarplantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction, seborrhoea, cold sweat, skin disorder nos, erythrosis, skin ulcer, nail disorder
Musculoskeletal and connective tissue disorders	
Frequent	Musculoskeletal pain, muscle spasms, pain in extremity, muscular weakness, arthralgia, bone pain, peripheral swelling, muscle cramps, myalgia, back pain
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, muscle stiffness, buttock pain

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Renal and urinary disorders	
Frequent	Renal impairment, dysuria
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, renal cholic, urinary frequency, loin pain, urinary incontinence
Reproductive system and breast disorders	
Less frequent	Vaginal haemorrhage, genital pain, erectile dysfunction, testicular disorder, prostatitis, female breast disorder, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders	
Less frequent	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions	
Frequent	Pyrexia, fatigue, asthenia, oedema (including peripheral), chills, pain, malaise, weakness, lethargy, rigors, peripheral oedema
Less frequent	General physical health deterioration, face oedema, injection site reaction, mucosal disorder, chest pain, gait disturbance, feeling cold, extravasation, catheter related complication, change in thirst, chest discomfort, feeling of body temperature change, injection site pain, death (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, mucosal inflammation, neuralgia
Investigations	
Frequent	Weight decreased; blood lactate dehydrogenase increased
Less frequent	Hyperbilirubinaemia, protein analyses abnormal, weight

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	increased, blood test abnormal, c-reactive protein increased, blood gases abnormal, electrocardiogram abnormalities (including QT prolongation), international normalised ratio abnormal, gastric pH decreased, platelet aggregation increased, troponin I increased, virus identification and serology, urine analysis abnormal, increased blood alkaline phosphatase, increased blood creatinine, increased blood urea, increased gamma glutamyl transferase, increased blood amylase, abnormal liver function tests, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, decreased blood phosphate
Injury, poisoning and procedural complications	
Less frequent	Fall, contusion, transfusion reaction, fractures, rigors, face injury, joint injury, burns, laceration, procedural pain, radiation injuries
Surgical and medical procedures	
Less frequent	Macrophage activation

*NOS: not otherwise specified

c. Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis decreases the incidence of herpes zoster.

Mantle cell lymphoma

Antiviral prophylaxis decreases the incidence of herpes zoster.

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

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HBV infection with fatal outcome was decreased when Bortezomib Adco was given in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.

Differences in the safety profile of subcutaneous administration versus intravenously as single medicine.

Subcutaneous administration:

Lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity and a lower incidence of discontinuation.

The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were lower.

In addition, the incidence of Grade 3 or higher peripheral neuropathies was lower, and the discontinuation rate due to peripheral neuropathies was lower for the subcutaneous as well

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 to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Overdosage is associated with acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. 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.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

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

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1,0 mg/m² and 1,3 mg/m² dose to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/ml

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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/m² dose and 89 to 120 ng/ml for the 1,3 mg/m² dose.

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/m² or 1,3 mg/m² 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 – 1 000 mg/ml.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent.

Elimination

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40 - 193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. 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.

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Special populations:

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

Age

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to paediatric patients (2-16 years old) with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7,79 (25 %) L/hr/m^2, volume of distribution at steady state was 834 (39 %) L/m^2, and the elimination half-life was 100 (44 %) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA normalized clearance of bortezomib in paediatric patients was similar to that observed in adults.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging from 0,5 to 1,3 mg/m². When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose- normalised bortezomib AUC. However, the dose normalised mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely.

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 m², n=12), Mild (CrCℓ=40-59 ml/min/1,73 m², n=10), Moderate (CrCℓ=20-39 ml/min/1,73 m², n=9), and Severe (CrCℓ < 20 ml/min/1,73 m², n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered

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intravenous doses of 0,7 to 1,3 mg/m2 of bortezomib twice weekly. Exposure of bortezomib (dose normalised AUC and Cmax) was comparable among all the groups (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (Pearlitol PF)

6.2 Incompatibilities

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

6.3 Shelf life

2 years

Infusion solutions

From a microbiological point of view, the medicine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours at 15 to 30 °C, unless reconstitution / dilution has taken place in a controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not refrigerate.

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

Do not freeze

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

6.5 Nature and contents of container

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10 ml clear tubular Type 1 glass vial with a grey rubber stopper and an aluminium flip-off seal with blue colour plastic disc.

6.6 Special precautions for disposal and other handling

For single use only.

Bortezomib Adco 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.

Reconstitution Instructions

Bortezomib Adco 3,5 mg is for IV or SC use.

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

Aseptic technique must be strictly observed throughout the handling of Bortezomib Adco, since no preservative is present.

Reconstitution for Intravenous administration

Each 10 ml vial of Bortezomib Adco must be carefully reconstituted with 3,5 ml of normal (0,9 %) saline.

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

	IV	SC
Volume of diluent (0,9 % Sodium Chloride) added to reconstitute one vial	3,5 ml	1,4 ml

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Final Concentration after reconstitution (mg/mL)	1,0 mg/ ml	2,5 mg/ ml

Dissolution is completed in less than 2 minutes. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted product must be discarded.

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

Any unused product or waste material should be disposed of in accordance with local requirements

Appearance of product after reconstitution: a clear and colourless solution free from visible particle matter.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road,

Aeroton,

Johannesburg, 2013

Tel: 011 494 8000

8. REGISTRATION NUMBER(S)

52/26/0727

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 August 2021

10. DATE OF REVISION OF THE TEXT

30 August 2024

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