Dr. Reddy's Laboratories (Pty) Ltd.
APPROVED PROFESSIONAL INFORMATION:
BERTRED 3,5
(Powder for solution for injection - Vial)

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BERTRED 3,5, 3,5 mg, lyophilised powder for solution for injection for intravenous and subcutaneous use

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Intravenous (IV) or subcutaneous (SC) use.

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

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

Excipient with known effect:

35,0 mg mannitol per vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilised powder for solution for injection.

Sterile white to off-white freeze-dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BERTRED 3,5 for injection is indicated for:

Multiple Myeloma

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation;
- in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation;

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

Mantle Cell Lymphoma

- treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.
- treatment for newly diagnosed mantle cell lymphoma (MCL) in adults, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Posology

BERTRED 3,5 lyophilised powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg /mL (as a 3 to 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.

BERTRED 3,5 IS FOR INTRAVENOUS AND SUBCUTANEOUS USE ONLY and should not be given by other routes. Intrathecal administration has resulted in death.

See section 6.6 for Reconstitution instructions.

BERTRED 3,5 re-treatment may be considered for multiple myeloma patients who had previously responded to treatment with BERTRED 3,5 (see below).

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended dosage

- The recommended starting dose of BERTRED 3,5 is 1,3 mg/m^2 body surface area (BSA) administered twice weekly for two weeks ([~~on~~] days 1, 4, 8, and 11), followed by a 10-day rest period (days 12 to 21).
- This 3-week period is considered a treatment cycle.
- It is recommended that patients receive 2 cycles of BERTRED 3,5 following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of therapy.
- At least 72 hours should elapse between consecutive doses of BERTRED 3,5.

Dose modification and re-initiation of treatment

BERTRED 3,5 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, BERTRED 3,5 treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2 or 1,0 mg/m^2 reduced to 0,7 mg/m^2).
- If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of BERTRED 3,5 must be considered unless the benefit of treatment clearly outweighs the risk.

The following table contains the recommended dose modification for the management of patients who experience BERTRED 3,5-related neuropathic pain and/or peripheral sensory neuropathy (Table 1). Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy may be treated with BERTRED 3,5 only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for BERTRED 3,5 related neuropathic pain and/or peripheral sensory neuropathy or motor neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting Instrumental Activities of Daily Living (ADL))[b]	Reduce BERTRED 3,5 to 1,0 mg/m^2 OR Change BERTRED 3,5 treatment schedule to 1,3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL[c])	Withhold BERTRED 3,5 therapy until toxicity resolves. When toxicity resolves re-initiate with a reduced dose of BERTRED 3,5 at 0,7 mg/m^2 once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue BERTRED 3,5

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

[a] Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

[b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money or other such daily activities.

[c] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Combination therapy

Previously untreated Multiple Myeloma - Patients who are not eligible for stem cell transplantation

Recommended dosage in combination with melphalan and prednisone

BERTRED 3,5 (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 to 4, BERTRED 3,5 is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32).

In cycles 5 to 9, BERTRED 3,5 is administered once weekly (days 1, 8, 22 and 29).

Table 2: Recommended dosage regimen for BERTRED 3,5 when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma who are not eligible for stem cell transplantation

Twice weekly BERTRED 3,5 (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
B (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

B= BERTRED M=Melphalan P= Prednisone

Once weekly BERTRED 3,5 (Cycles 5 to 9)									
Week	**1**				**2**	**3**	**4**	**5**	**6**
B (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

B= BERTRED 3,5 M=Melphalan P= Prednisone

Dose management guidelines for combination therapy with melphalan and prednisone

Dose modification and re-initiation of therapy when BERTRED 3,5 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 absolute neutrophil count (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 is ≤ 30 x 10^9/L or ANC is ≤ 0,75 x 10^9/L on a BERTRED 3,5 dosing day (other than Day 1)	BERTRED 3,5 dose should be withheld.
If several BERTRED 3,5 doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	BERTRED 3,5 dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1,0 mg/m^2 to 0,7 mg/m^2).
Grade > 3 non-haematological toxicities	BERTRED 3,5 therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BERTRED 3,5 may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1,0 mg/m^2 to 0,7 mg/m^2). For BERTRED 3,5-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BERTRED 3,5 dose as outlined in Table 1.

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

Previously untreated Multiple Myeloma – Patients who are eligible for stem cell transplantation

Recommended Dosage

The recommended starting dose of BERTRED 3,5 in combination with other medicines used for the treatment of multiple myeloma is 1,3 mg/m^2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10 to 18 days, which is considered a treatment cycle.

Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of BERTRED 3,5.

For BERTRED 3,5 dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (Table 1) above.

For dosing instructions for other medicines combined with BERTRED 3,5, see their respective professional information leaflets.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin

For BERTRED 3,5 dosage and dose modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the BERTRED 3,5 3-week regimen as a 1-hour intravenous infusion administered after the BERTRED 3,5 injection. For additional information concerning pegylated liposomal doxorubicin, see respective professional information leaflet.

Recommended Dosage in Combination with Dexamethasone

For BERTRED 3,5 dosage and dose modifications, see Monotherapy.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, BERTRED 3,5 administration.

For additional information concerning dexamethasone, see respective professional information leaflet.

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with BERTRED 3,5 (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to Monotherapy for dosing schedule.

Previously untreated Mantle Cell Lymphoma

Recommended dosage in combination with rituximab, cyclophosphamide, doxorubicin and prednisone

For BERTRED 3,5 dosage, see Monotherapy. Six BERTRED 3,5 cycles are administered. For patients with a response first documented at Cycle 6, two additional BERTRED 3,5 cycles are recommended.

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

Dose Adjustments during treatment for patients with previously untreated Mantle Cell Lymphoma

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

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1,5 x 10^9/L
- Haemoglobin should be ≥ 8 g/dL (≥ 4,96 mmol/L)
- Non-haematologic toxicity should have recovered to Grade 1 or baseline

BERTRED 3,5 treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 3 haematological toxicities, excluding neuropathy (see also section 4.4). For dose adjustments, see Table 4 below.

Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 4: Dose adjustments during treatment for patients with previously untreated Mantle Cell Lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity	
• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x 10^9/L	BERTRED 3,5 therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L. • If, after BERTRED 3,5 has been held, the toxicity does not resolve, as defined above, then BERTRED 3,5 must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, BERTRED 3,5 dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2).
• If platelet counts < 25 x 10^9/L or ANC < 0,75 x 10^9/L on a BERTRED 3,5 dosing day (other than Day 1)	BERTRED 3,5 dose should be withheld
Grade ≥ 3 non-haematological toxicities	BERTRED 3,5 therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BERTRED 3,5 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 BERTRED 3,5-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BERTRED 3,5 as outlined in Table 1.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see the respective professional information leaflet.

Special populations

Paediatric patients

BERTRED 3,5 has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (older than 65 years) with multiple myeloma or with mantle cell lymphoma (see section 4.8).

Patients with Renal Impairment

The pharmacokinetics of BERTRED 3,5 are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 mL/min/1,73 m^2). Therefore, dosing adjustments of BERTRED 3,5 are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce BERTRED 3,5 concentrations, BERTRED 3,5 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 BERTRED 3,5 dose. Patients with moderate or severe hepatic impairment should be started on BERTRED 3,5 at a reduced dose of 0,7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see Table 5).

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

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

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

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

Method of Administration

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

Administration precautions

There have been fatal cases of inadvertent administration of BERTRED 3,5.

DO NOT ADMINISTER BERTRED 3,5 INTRATHECALLY.

BERTRED 3,5 is for single use only. Discard any unused portions.

BERTRED 3,5 is for IV or SC use.

Intravenous injection:

The reconstituted solution is administered as a 3 to 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 BERTRED 3,5.

Subcutaneous injection:

When administered subcutaneously, alternate sites for each injection (thigh or abdomen).

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

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.

If local injection site reactions occur following BERTRED 3,5 injection subcutaneously, a less concentrated BERTRED 3,5 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 of BERTRED 3,5.

Acute diffuse infiltrative pulmonary disease or pericardial disease.

4.4 Special warnings and precautions for use

Herpes zoster virus reactivation:

Medical practitioners should consider the need for antiviral prophylaxis in patients being treated with BERTED 3,5.

In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with bortezomib, Melphalan and Prednisone.

Hepatitis B Virus (HBV) reactivation and infection:

When rituximab is used in combination with BERTRED 3,5, 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 BERTRED 3,5. Antiviral prophylaxis should be considered. Refer to the Professional Information of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML):

Cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of 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 BERTRED 3,5 if PML is diagnosed.

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, BERTRED 3,5 should be discontinued. The safety of reinitiating BERTRED 3,5 therapy in patients previously experiencing PRES is not known.

Concomitant medicines:

Patients should be closely monitored when given BERTRED 3,5 in combination with potent CYP3A4-inhibitors. Caution should be exercised when BERTRED 3,5 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 hypoglycaemics (see section 4.5).

Haematological toxicity:

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is an

less frequent undesirable effect. The most frequent haematologic toxicity is 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 count decrease, and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Platelet counts should be monitored prior to each dose of BERTRED 3,5. Therapy should be withheld when the platelet count is < 25,000/µL, or in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/ µL (see sections 4.2 and 4.8). Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematological toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

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

Table 6: Severity of thrombocytopenia related to pre-treatment platelet count in the Phase 3 Multiple Myeloma study of bortezomib vs. dexamethasone

Pre-treatment Platelet Count[a]	**Number of Patients (N=331) b**	**Number of Patients with Platelet Count < 10,000/µL**	**Number of Patients with Platelet Count 10,000 to 25,000/µL**
≥ 75,000/µL	309	8 (3 %)	36 (12 %)
≥ 50,000/µL to < 75,000/µL	14	2 (14 %)	11 (79 %)
≥ 10,000/µL to	7	1 (14 %)	5 (71 %)

< 50,000/µL			

[a] baseline platelet count of 50,000/µL was required for study eligibility.

[b] Data for one patient was missing at baseline.

In the combination study of bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone (BR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was 32 % BR-CAP vs. 2 % for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ Grade 3) was 1,7 % (4 patients) in the BR-CAP arm and was 1,2 % (3 patients) in the R-CHOP arm.

There were no deaths due to bleeding events in either arm. There were no CNS bleeding events in the BR-CAP arm; there was 1 bleeding event in the R-CHOP arm. Platelet transfusions were given to 23 % of the patients in the BR-CAP arm and 3 % of the patients in the R-CHOP arm.

The incidence of neutropenia (≥ Grade 4) was 70 % in the BR-CAP arm and 52 % in the R-CHOP arm. The incidence of febrile neutropenia (≥ Grade 4) was 5 % in the BR-CAP arm and 6 % in the R-CHOP arm. Colony-stimulating factor support was provided at a rate of 78 % in the BR-CAP arm and 61 % in the R-CHOP arm.

Gastrointestinal toxicity:

Diarrhoea, constipation, nausea and vomiting, occur frequently with BERTRED 3,5 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-diarrhoeal medication. Fluid and electrolyte replacement should be given to prevent or treat dehydration.

Cases of ileus have been reported, therefore patients who experience constipation should be closely monitored.

Peripheral neuropathy:

Bortezomib 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 [BERTRED 3,5]

bortezomib.

The incidence of peripheral neuropathy increases early in the treatment and has

been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy

such as a burning sensation, hyperaesthesia, hypoaesthesia, paraesthesia,

discomfort or neuropathic pain. Patients experiencing new or worsening peripheral

neuropathy may require the dose and schedule of BERTRED 3,5 to be modified

(see section 4.2). Neuropathy has been managed with supportive care and other therapies.

Peripheral neuropathy may not be reversible.

Improvement in, or resolution of, peripheral neuropathy was reported in 51 % of patients

with ≥ Grade 2 peripheral neuropathy in the single medicine phase III multiple

myeloma study of bortezomib vs. dexamethasone and 73 % of patients with grade 3 or

4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase II studies,

respectively.

In addition to peripheral neuropathy, there may be a contribution of autonomic

neuropathy to some adverse reactions such as postural hypotension and severe

constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

The long-term outcome of peripheral neuropathy has not

been studied in Mantle Cell Lymphoma.

Seizures:

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

Hypotension:

Bortezomib treatment is associated with orthostatic/postural hypotension. Most patients require treatment for their orthostatic hypotension. Patients with orthostatic hypotension may experience syncopal events. The mechanism of this event is unknown, although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib and 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 monitored closely. Fluid retention may be a predisposing factor for signs and symptoms of heart failure.

There have been isolated cases of QT-interval prolongation; causality has not been established. Patients using angiotensin inhibitors, beta-blockers, antihypertensive medicine, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during bortezomib treatment.

Pulmonary disorders:

Unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) have been reported in patients receiving bortezomib. Some of these events have been fatal. A higher

proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be

performed and patients treated appropriately.

In a clinical trial, the first two patients who received high-dose cytarabine (2 g/m2 BSA

per day) by continuous infusion in combination with daunorubicin and bortezomib

(such as in BERTRED 3,5) for relapsed acute myelogenous leukaemia, died of ARDS

early in the course of therapy. The trial was discontinued subsequently and this specific treatment regimen is not recommended.

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 BERTRED 3,5. There is limited re-challenge information in these patients.

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 BERTRED 3,5 at reduced starting doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Tumour lysis syndrome (TLS):

Because BERTRED 3,5 is a cytotoxic medicine and can rapidly kill malignant plasma cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrrhythmias and syncope. These patients should be monitored closely and appropriate precautions taken.

Amyloidosis:

The impact of proteasome inhibition by BERTRED 3,5 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 less frequently. BERTRED 3,5 should be discontinued if severe reactions occur.

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

4.5 Interaction with other medicines and other forms of interaction

Bortezomib as in BERTRED 3,5 is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4 *in vitro*.

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 BERTRED 3,5.

Co-administration of bortezomib and ketoconazole, a potent CYP3A4 inhibitor, increased the mean AUC of bortezomib by 35 %. Patients receiving potent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir together with BERTRED 3,5, should be monitored closely.

Concomitant use of bortezomib with rifampicin, a potent CYP3A4 inducer, showed a mean bortezomib AUC reduction of 45 %. Therefore, the concomitant use of BERTRED 3,5 with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbitone and St. John's Wort) is not recommended, as efficacy may be reduced.

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

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

Concomitant administration of melphalan and prednisone with bortezomib, as contained in BERTRED 3,5, increased the mean bortezomib AUC by 17 %. This is not considered to be clinically relevant.

Hypoglycaemia and hyperglycaemia were reported in diabetic patients who received oral hypoglycaemic medicines with bortezomib, as contained in BERTRED 3,5.

The blood glucose levels of patients on oral anti-diabetic medicines should be monitored closely if treated with BERTRED 3,5. The dosages of anti-diabetic medicines may require adjustment in these patients.

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

Pregnancy

Safety in pregnancy has not been established.

If BERTRED 3,5 is used during pregnancy, alone or in combination with other medicines, or if the patient becomes pregnant while receiving BERTRED 3,5, the patient needs to be informed of the potential hazards to the foetus.

Breastfeeding

Safety in lactation has not been established.

It is not known whether BERTRED 3,5 is excreted in human milk. Because of the potential for serious undesirable effects in breast-fed infants from BERTRED 3,5, women are advised against breastfeeding while receiving BERTRED 3,5.

Contraception in males and females

Males and females of childbearing capacity must use effective contraceptive measures during treatment and for 3 months following BERTRED 3,5 therapy.

4.7 Effects on ability to drive and use machines

BERTRED 3,5 may have a moderate influence on the ability to drive and use machines. BERTRED 3,5 may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when driving, or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions less frequently reported during treatment with 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.

Adverse reactions reported with bortezomib are listed below by system organ class and frequency grouping.

Table 7: Side effects in patients with Multiple Myeloma treated with bortezomib, as a single medicine or in combination:

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Frequent	Herpes zoster (inc. disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Less frequent	Infection*, Bacterial infections*, Viral infections*, Sepsis (including. septic shock)*, Bronchopneumonia, Herpes virus infection*, Bacteraemia (including staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*

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*, Leukocytosis*, Lymphadenopathy, Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Less frequent	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*
	Less frequent	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention, Hypermagnesaemia*,

		Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Frequent	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Less frequent	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness, Suicidal ideation*, Adjustment disorder, Delirium, Decreased libido
Nervous system disorders	Frequent	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*, Motor neuropathy*, Loss of consciousness (including syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Less frequent	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (excluding dementia)*, Encephalopathy*, Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, 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
Eye disorders	Frequent	Eye swelling*, Abnormal vision*, Conjunctivitis*
	Less frequent	Eye haemorrhage*, Eyelid infection*, Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Increased lacrimation, Eye discharge, Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (including eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, 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
Cardiac disorders	Less frequent	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
Vascular disorders	Frequent	Hypotension*, Orthostatic hypotension, Hypertension*
	Less frequent	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), Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract 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 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, Gastrooesophageal reflux disease*, Colitis (including clostridium difficile)*, 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
Hepatobiliary	Frequent	Hepatic enzyme abnormality*

disorders	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, Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Acne*, Blister*, Pigmentation disorder*, Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal pain*, 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	Frequent	Renal impairment*

disorders	Less frequent	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria, Bladder irritation
Reproductive system and breast disorders	Less frequent	Vaginal haemorrhage, Genital pain*, Erectile dysfunction, Testicular disorder*, Prostatitis, 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*, 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	Decreased weight
	Less frequent	Hyperbilirubinaemia*, Abnormal protein analyses*, Increased weight, Abnormal blood

		test*, Increased C-reactive protein, Abnormal blood gases*, Electrocardiogram abnormalities (including QT prolongation)*, Abnormal International Normalised Ratio* (INR), Decreased gastric pH, Increased platelet aggregation, Increased Troponin I, Virus identification and serology*, Abnormal urine analysis*
Injury, poisoning and procedural complications	Frequent	Fall, Contusion
	Less frequent	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Frequent	Macrophage activation

NOS=not otherwise specified

* Grouping of more than one MedDRA preferred term.

Patients with mantle cell lymphoma (MCL)

The safety profile of bortezomib observed in these patients is similar to patients with multiple myeloma but with the following notable differences:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia were reported more often in multiple myeloma than in mantle cell myeloma while peripheral neuropathy, rash and pruritus occurred more often in patients with mantle cell lymphoma.

Table 8: Adverse reactions in patients with Mantle Cell Lymphoma treated with BR-CAP

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Frequent	Pneumonia*, Sepsis (including septic shock)*, Herpes zoster (including disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Less frequent	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Frequent	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Less frequent	Pancytopenia*
Immune system disorders	Frequent	Hypersensitivity*
	Less frequent	Anaphylactic reaction
Metabolism and nutrition disorders	Frequent	Decreased appetite, Hypokalaemia*, Abnormal blood glucose*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Less frequent	Tumour lysis syndrome
Psychiatric disorders	Frequent	Sleep disorders and disturbances*
Nervous system disorders	Frequent	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*, Neuropathies*, Motor neuropathy*, Loss of consciousness (including syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Less frequent	Autonomic nervous system imbalance
Eye disorders	Frequent	Abnormal vision*

Ear and labyrinth disorders	Frequent	Dysacusis (inc. tinnitus)*
	Less frequent	Vertigo*, Hearing impaired (up to and including deafness)
Cardiac disorders	Frequent	Cardiac fibrillation (including atrial), Arrhythmia*, Cardiac failure (inc. left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Less frequent	Cardiovascular disorder (including cardiogenic shock)
Vascular disorders	Frequent	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea*, Cough*, Hiccups
	Less frequent	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (including acute)
Gastrointestinal disorders	Frequent	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation, Gastrointestinal haemorrhage (including mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc. gastrointestinal and splenic pain)*, Oral disorder*
	Less frequent	Colitis (including clostridium difficile)*
Hepatobiliary disorders	Frequent	Hepatotoxicity (including liver disorder)
	Less frequent	Hepatic failure
Skin and Subcutaneous tissue disorders	Frequent	Hair disorder*, Pruritus*, Dermatitis*, Rash*

Musculoskeletal and connective tissue disorders	Frequent	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Frequent	Urinary tract infection*
General disorders and administration site conditions	Frequent	Pyrexia*, Fatigue, Asthenia
		Oedema (inc. peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Frequent	Hyperbilirubinaemia*, Abnormal protein analyses*, Decreased weight, Increased weight

* Grouping of more than one MedDRA preferred term.

Description of selected adverse reactions

Herpes zoster virus reactivation

Herpes zoster reactivation was reported to occur more frequently in patients who received bortezomib combined with melphalan and prednisone, compared with patients who received only melphalan and prednisone.

Herpes zoster reactivation was, however, similar to that of only melphalan and prednisone when patients received prophylactic antivirals with bortezomib, melphalan and prednisone combination therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage was associated with acute onset of symptomatic hypotension and thrombocytopenia and the patient subsequently died. It is recommended that in the event of overdosage, patients should undergo careful haemodynamic monitoring, and hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents.

Mechanism of action

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

The 26S proteasome is a large protein complex that degrades ubiquitinated proteins.

The ubiquitin-proteasome pathway plays an essential part in orchestrating 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 cell death.

Bortezomib is highly selective for the proteasome. A wide variety of receptors and proteases screened for inhibition by bortezomib (at 10 µM concentration), did not show any and bortezomib was shown to be more than 1500-fold more selective for the proteasome than for its next preferable enzyme.

In vitro kinetic studies of proteasome inhibition showed that bortezomib dissociates from the proteasome with a $t_{½}$ of 20 minutes, indicating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-κB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-κB 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 doses of 1,0 and 1,3 mg/m^2 body surface area (BSA) to patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mL respectively after the first dose. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1,0 mg/m^2 BSA dose and 89 to 120 ng/mL for the 1,3 mg/m^2 BSA dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 t0 193 hours.

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 BSA, respectively, and ranged from 15 to 32 l/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2 BSA, respectively.

Distribution

The mean volume distribution of bortezomib is variable and ranged from 1659 litres to 3294 litres following administration of single-and repeat-doses of 1,0 or 1,3 mg/m^2 BSA 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 to 1000 mg/mL.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozy**m**es 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.

Plasma levels of these metabolites are low compared to the parent substance**.**

Elimination

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40 to 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.

Special populations

Age, Gender and Race

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 to 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-normalised clearance of bortezomib in paediatric patients was similar to that observed in adults.

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

Hepatic impairment

The effect of hepatic impairment (see Table 5 for hepatic impairment classification) on the pharmacokinetics of bortezomib was assessed in 61 cancer patients at bortezomib doses ranging from 0,5 to 1,3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose- 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 (see Table 5).

Renal impairment

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Nitrogen

Tertiary butanol

Water for injection

6.2 Incompatibilities

BERTRED 3,5 must not be mixed with other medicinal products 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.

From a microbiological point of view the product 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 24 hours at 2 to 8° C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 30 ºC and 15 days at 2 °C to 8 °C, stored in the original vial and/or a syringe prior to administration.

6.4 Special precautions for storage

Store at or below 30 ºC. Keep the vial in the outer carton in order to protect from light.

KEEP OUT OF REACH OF CHILDREN**.**

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

6.5 Nature and contents of container

BERTRED 3,5 is supplied in a single-use 10 mL type I, clear, colourless, flint tubular glass vial, stoppered with a 13 mm dark grey coloured bromobutylrubber stopper and sealed with 13 mm royal blue coloured aluminium flip-off seal, packed in an outer printed cardboard carton.

6.6 Special precautions for disposal and other handling

BERTRED 3,5 is a cytotoxic medicine. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST STRICTLY BE OBSERVED THROUGHOUT HANDLING OF BERTRED 3,5 SINCE NO PRESERVATIVE IS PRESENT.

Reconstitution instructions:

- BERTRED 3,5 is provided as a lyophilised powder in the form of a mannitol boronic ester.
- When reconstituted, the mannitol ester is in equilibrium with its hydrolysis product, the monomeric boronic acid.

Reconstitution for intravenous administration

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

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

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

	IV	**SC**
	(3,5 mg bortezomib)	(3,5 mg bortezomib)
Volume of diluent (0,9 % sodium chloride) added to reconstitute one vial	3,5 mL	1,4 mL
Final concentration after reconstitution (mg/mL)	1,0 mg/mL	2,5 mg/mL

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER

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