Professional Information for BOTIGEN 3,5

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BOTIGEN 3,5

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

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

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

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

Excipients

Contains sugar (Mannitol 35 mg per vial)

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection

BOTIGEN 3,5 is a white to off white lyophilized cake or powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTIGEN 3,5 for injection is indicated in adult patients as:

Multiple Myeloma

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

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

BOTIGEN 3,5 is for IV or SC use only.

DO NOT ADMINISTER BOTIGEN 3,5 INTRATHECALLY.

BOTIGEN 3,5 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.

BOTIGEN 3,5 should not be given by other routes.

Intrathecal administration has resulted in death.

For instructions on dilution of BOTIGEN 3,5 prior to administration, see section 6.6.

See Reconstitution Instructions below.

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

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended dosage

The recommended starting dose of BOTIGEN 3,5 is 1,3 mg/m^2 body surface area administered 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. It is recommended that patients receive 2 cycles of BOTIGEN 3,5following 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 BOTIGEN 3,5.

Recommended dosage adjustments during treatment and re-initiation of treatment

BOTIGEN 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 section 4.4). Once the symptoms of the toxicity have resolved, BOTIGEN 3,5 treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2; 1,0 mg/m^2 reduced to 0,7 mg/m^2).

If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of BOTIGEN 3,5 must be considered.

The following table contains the recommended doe modification for the management of patients who experience BOTIGEN3,5 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 BOTIGEN 3,5 only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for BOTIGEN 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, paraesthesia, weakness and/or loss of reflexes) with no 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 to 1.0 mg/m^2 OR Change BOTIGEN 3,5treatment 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 BOTIGEN 3,5 therapy until toxicity resolves. When toxicity resolves re-initiate with a reduced dose of BOTIGEN 3,5 at 0,7 mg/m^2 once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue BOTIGEN 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

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

Table 2: Recommended Dosage Regimen for BOTIGEN 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 BOTIGEN 3,5(Cycles 1-4)

Week	**1**	**2**	**3**	**4**	**5**	**6**
Vc (1,3 mg/m^2)	Day---- Day 1 4	Day Day 8 11	rest period	Day Day 22 25	Day Day 29 32	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day Day Day Day 1 2 3 4	-- --	Rest period	-- --	-- --	rest period

Once Weekly BOTIGEN 3,5 (Cycles 5-9)

Week	**1**	**2**	**3**	**4**	**5**	**6**
PN (1,3 mg/m^2)	Day -- -- -- 1 4	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m^2)	Day Day Day Day 1 2 3 4	--	Rest period	--	--	rest period

p (60 mg/m^2)						

PN = BOTIGEN 3,5 3,5; m = melphalan, p=prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone

Dose modification and re-initiation of therapy when BOTIGEN 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 the 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 ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a BOTIGEN 3,5 dosing day (other than day 1)	BOTIGEN 3,5 dose should be withheld
- If several BOTIGEN 3,53, 5 doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	BOTIGEN 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

Grade ≥ 3 non-haematological toxicities	BOTIGEN 3,5 therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then BOTIGEN 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 BOTIGEN 3,5-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BOTIGEN 3,5 as outlined in Table 1.

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

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

Recommended Dosage

The recommended starting dose of BOTIGEN 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 10-18 days, which is considered a treatment cycle. Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of BOTIGEN 3,5.

For BOTIGEN 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 BOTIGEN 3,5, see their respective professional information leaflets.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin

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

Pegylated liposomal doxorubicin is administered at 30 mg/m^2 on day 4 of the BOTIGEN 3,5 3-week regimen as a 1-hour intravenous infusion administered after the BOTIGEN 3,5 injection.

For additional information concerning pegylated liposomal doxorubicin, see respective professional information leaflet.

Recommended Dosage in Combination with Dexamethasone

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

Dexamethasone is administered orally at 20 mg on the day of, and the day after, BOTIGEN 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 BOTIGEN 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 BOTIGEN 3,5 dosage, see Monotherapy. Six BOTIGEN 3,5 cycles are administered. For patients with a response first documented at Cycle 6, two additional BOTIGEN 3,5 cycles are recommended.

The following medicines are administered on Day 1 of each BOTIGEN 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

BOTIGEN 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	BOTIGEN 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 BOTIGEN 3,5 has been held, the toxicity does not resolve, as defined above, then BOTIGEN 3,5 must be discontinued. • If toxicity resolves i.e., patient has anANC ≥ 0,75x 10^9/L and a platelet count ≥ 25 x 10^9/L,BOTIGEN 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 BOTIGEN 3,5dosing day (other than Day 1)	BOTIGEN 3,5 dose should be withheld
Grade ≥ 3 non-haematological toxicities	BOTIGEN 3,5 therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BOTIGEN 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 BOTIGEN 3,5-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BOTIGEN 3,5as outlined in Table 1.

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

Special populations

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 BOTIGEN 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 BOTIGEN 3,5are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce BOTIGEN 3,5concentrations, BOTIGEN 3,5should 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 BOTIGEN 3,5 dose. Patients with moderate or severe hepatic impairment should be started on BOTIGEN 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, section 4.4 and 5.2).

Table 5: Recommended Starting Dose Modification for BOTIGEN 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 BOTIGEN 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).

Paediatric patients

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

Method of administration

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

Administration Precautions

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

DO NOT ADMINISTER BOTIGEN 3,5 INTRATHECALLY.

Intravenous injection:

The reconstituted solution is administered as a 3 - 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of BOTIGEN 3,5.

Subcutaneous injection:

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

If local injection site reactions occur following BOTIGEN 3,5 injection subcutaneously, a less concentrated BOTIGEN3,5 solution (1 mg/mL instead of 2,5 mg/mL) may be administered subcutaneously, or changed to IV injection.

4.3 Contraindications

- Hypersensitivity to BOTIGEN 3,5, boron or to any of the excipients (see section 6.1).
- Acute diffuse infiltrative pulmonary and pericardial disease.
- When BOTIGEN 3,5 is given in combination with other medicines, refer to their Professional Information Leaflet for additional contraindications.

4.4 Special warnings and precautions for use

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

When BOTIGEN 3,5 is given in combination with other medicines, the Professional Information Leaflet of these other medicines must be consulted prior to initiation of treatment with BOTIGEN 3,5. When

thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of BOTIGEN 3,5. BOTIGEN 3,5 powder for solution for injection is for intravenous or subcutaneous use only.

DO NOT ADMINISTER BOTIGEN 3,5 INTRATHECALLY.

Herpes Zoster Virus Reactivation

Medical practitioners should reconsider using antiviral prophylaxis in patients being treated with BOTIGEN 3,5.

The overall incidence of herpes zoster reactivation was very common in patients treated with BOTIGEN 3,5.

Patients with mantle cell lymphoma:

Overall, the safety profile of patients treated with BOTIGEN 3,5 in monotherapy was similar to that observed in patients treated with BOTIGEN 3,5 in combination with melphalan and prednisone.

Laboratory Tests

Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with BOTIGEN 3,5.

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are frequent with BOTIGEN 3,5treatment (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

BOTIGEN 3,5 treatment is frequently associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of BOTIGEN 3,5 treatment and typically recovered to baseline by the next cycle.

The cyclical pattern of platelet decrease and recovery remained consistent over the 8 cycles of twice weekly dosing and there was no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

The mean platelet count nadir measured was approximately 40 % of baseline.

Severe bleeding, including CNS and gastrointestinal bleeding, associated with thrombocytopenia, has been reported.

In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count (see table 5). Platelet counts should be monitored prior to each dose of BOTIGEN 3,5. Therapy should be held 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).

Potential benefit of the treatment should be carefully weighed against the risks.

Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities.

Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Table 5: The Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Phase 3 Study Multiple Myeloma Study of bortezomib vs Dexamethasone

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

* Data for one patient was missing at baseline.

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

Peripheral neuropathy

Treatment with BOTIGEN 3,5 causes a peripheral neuropathy (PN), which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported.

Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with BOTIGEN 3,5.

The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

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

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require change in the dose, schedule or route of administration of BOTIGEN 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.

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 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 commonly associated with orthostatic/postural hypotension.

Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events.

Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib.

The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to BOTIGEN 3,5 or BOTIGEN 3,5 may aggravate an underlying condition such as diabetic neuropathy.

Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineral corticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Cardiac Disorders

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

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

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

Pulmonary Disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving BOTIGEN 3,5 (see section 4.8). 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.

Specific treatment regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Renal impairments

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see section 4.2 and 5.2).

Hepatic Events

Rare cases of hepatic failure have been reported in patients receiving BOTIGEN 3,5 and concomitant medicines and with serious underlying medical conditions. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of BOTIGEN 3,5 (see section 4.8). There is limited re-challenge information in these patients.

Hepatic Impairment

BOTIGEN 3,5 is metabolised by liver enzymes. BOTIGEN 3,5 exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with BOTIGEN 3,5 at reduced starting doses and closely monitored for toxicities. See sections 4.2 and 5.2.

Tumour lysis syndrome

Because BOTIGEN 3,5 is a cytotoxic agent 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 BOTIGEN 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 uncommonly. BOTIGEN 3,5 should be discontinued if severe reactions occur.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving bortezomib.

PRES is a rare, often 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 BOTIGEN 3,5.

The safety of reinitiating BOTIGEN 3,5 therapy in patients previously experiencing PRES is not known.

Concomitant medicines

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib 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 hypoglycemics (see section 4.5).

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 BOTIGEN 3,5 if PML is diagnosed.

4.5 Interaction with other medicines and other forms of interaction

Bortezomib is a weak inhibitor of cytochrome P450 (CYP) isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4.

Based on the limited contribution (7 %) of CYP2D6 to the metabolism of bortezomib the CYP2D6, poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

Ketoconazole (a potent CYP3A4 inhibitor) increased exposure to bortezomib. Therefore, patients should be monitored closely when given BOTIGEN 3,5in combination with potent CYP3A4 inhibitors (e.g. ketoconazole and ritonavir).

However, omeprazole (a potent CYP2C19 inhibitor) did not increase exposure to bortezomib.

Patients should be closely monitored for toxicities or reduced efficacy when BOTIGEN 3,5 is given with inhibitors or inducers of CYP3A4.

The concomitant use of BOTIGEN 3,5 with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

Although melphalan plus prednisone increased exposure to BOTIGEN 3,5, the increase is not thought to be clinically relevant.

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

Hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving BOTIGEN 3,5 treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics.

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

Women of childbearing potential / Contraception in males and females:

Male patients should be advised to use highly effective contraception, until the end of relevant

systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days (i.e., 60-75 days for sperm production plus 10-14 days for the transport to epididymis). Men must be advised to use effective methods of contraception and not to father a child during treatment with gemcitabine and in the 3 months following its discontinuation.

Female patients and female sexual partners of male patients receiving genotoxic anticancer

medicines, should be advised to use highly effective contraception, until the end of relevant

systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis). Due to the genotoxic potential of gemcitabine, women of childbearing age must use effective contraception during treatment with gemcitabine and for 6 months after treatment discontinuation.

Pregnancy:

Safety in pregnancy and lactation has not been established.

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

Thalidomide is a known human teratogenic active medicine that causes severe life-threatening birth defects. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the thalidomide pregnancy prevention programme are met. Patients receiving BOTIGEN 3,5 in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide. Refer to the Professional Information of thalidomide for additional information.

Breastfeeding:

It is not known whether BOTIGEN 3,5 is excreted in human milk. Because of the potential for serious undesirable effects in breast-fed infants from BOTIGEN 3,5 women should not breastfeed their infants while receiving BOTIGEN 3,5.

Fertility

There is no data on fertility.

4.7 Effects on ability to drive and use machines

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

BOTIGEN 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 reported 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 autonomic neuropathy.

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

Tabulated summary of adverse events

The following side effects have been reported:

System Organ Class	**Incidence**	**Adverse reactions**
Infections and infestations	*Frequent*	Herpes zoster (including disseminated & ophthalmic). Pneumonia*, herpes simplex*, fungal infection*
	Less frequent	Sepsis (inc. septic shock)*, bacteraemia (inc. staphylococcal), bronchopneumonia, cytomegalovirus infection, influenza infection*, bacterial infection*,viral

		infection*,inappantidiairus infection*, meningngoencephalitis herpetic*hordeolum, cellulitis, device related infection, skin infection*, ear infection*, staphylococcal infection, tooth infection*,meningitis (incl. bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome
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 (see Warnings and Special Precautions) (See section 4.4)	*Frequent*	Thrombocytopenia*, neutropenia*, anemia*, leukopenia*, lymphopenia*.
	Less Frequent	Pancytopenia*, febrile neutropenia, haemolytic anaemia#, thrombotic microangiopathy (inc. thrombocytopenic purpura)#, lymphadenopathy, coagulopathy*, leucocytosis*, Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration

Immune system disorders	*Less Frequent*	Hypersensitivity*, Type III immune complex mediated reaction, anaphylactic shock, amyloidosis, angioedema#.
Endocrine disorders	*Less Frequent*	Inappropriate antidiuretic hormone (ADH) secretion, Cushing's syndrome*, hyperthyroidism*, hypothyroidism
Metabolism and nutrition disorders	*Frequent*	Appetite decreased, dehydration, hypokalaemia*, hyponatraemia*, blood glucose abnormal*, hypocalcaemia*, enzyme abnormality*.
	Less Frequent	Hyperkalaemia*, hypercalcaemia*, hypernatraemia*, vitamin B12 deficiency, appetite increased, hypomagnesaemia*, hypophosphataemia*, tumour lysis syndrome, failure to thrive*, uric acid abnormal*, diabetes mellitus*, fluid retention hypermagnesaemia*, acidosis, electrolyte imbalance*, fluid overload, hypochloraemia*, hypovolaemia, hyperchloraemia*, hyperphosphataemia, metabolic disorder, vitamin B complex deficiency, gout, alcohol intolerance.

Psychiatric disorders	*Frequent*	Depression, insomnia, confusion, anxiety disorders*, mood disorders and disturbances*, sleep disorders and disturbances*.
	Less Frequent	Delirium, hallucinations*, restlessness, mental disorder*, psychotic disorder*, suicidal ideation*, adjustment disorder, libido decreased' agitation.
Nervous system disorders	*Frequent*	Peripheral sensory neuropathy, headache*, dizziness*, dysgeusia*, dysaesthesia*, neuropathies*, neuralgia*, loss of consciousness (inc. syncope), lethargy.
	Less frequent	Tremor, intracranial haemorrhage (inc. subarachnoid)*, -peripheral sensorimotor neuropathy, paresis*, disturbance in attention, migraine, cognitive disorder NOS, sciatica, speech disorder*, restless leg syndrome, dyskinesia*, cerebellar coordination and balance disturbances*, memory loss (exc. dementia)*, encephalopathy*, posterior reversible encephalopathy syndrome#, neurotoxicity seizure disorders*, post herpetic neuralgia, reflexes abnormal*, parosmia,

		cerebral haemorrhage*, brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, autonomic neuropathy, cranial palsy*, paralysis* presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, motor dysfunction, nervous system disorder NOS, radiculitis, drooling, hypotonia, Guillain-Barre syndrome#, demyelinating polyneuropathy#.
Eye disorders	*Frequent*	Eye swelling*, vision abnormal*, vision blurred, Conjunctivitis*
	Less Frequent	Eye haemorrhage*, eye discharge, photophobia, eye irritation*, lacrimation increased, eyelid infection*, chalazion#, blepharitis#, eye inflammation*, diplopia, dry eye*, eye pain, corneal lesion*, exophthalmos, retinitis, scotoma, eye disorder (inc. eyelid) NOS, dacryoadenitis acquired, photopsia, optic neuropathy#, different degrees of visual impairment (up to blindness)*.
	Frequent	Vertigo*.

Ear and labyrinth disorders	*Less Frequent*	Dysacusis (inc. tinnitus)*, hearing impaired (up to and inc. deafness), ear discomfort*,Ear haemorrhage, vestibular neuronitis, Ear disorder NOS, hypoacusis
Cardiac disorders	*Less Frequent*	Cardiovascular disorder (inc. cardiogenic shock), cardiac arrest, development or exacerbation of congestive heart failure (See section 4.4), ventricular hypokinesia, myocardial infarction, unstable angina pectoris, cardiac failure (inc. left and right ventricular)*, , sinus arrest, complete atrioventricular block*, tachycardia*, cardic tamponade#, cardio-pulmonary arrest*, arrhythmia, angina pectoris, pericarditis (inc. pericardial effusion)*, cardiomyopathy, ventricular dysfunction, bradycardia, atrial flutter, myocardial infarction*, torsade de pointes, cardiac valve disorders*, coronary artery insufficiency, cardiac fibrillation (inc. atrial), palpitations, sinus tachycardia, supraventricular tachycardia, dysrhythmia.

Vascular disorders	*Frequent*	Hypotension*, orthostatic and postural hypotension (See section 4.4), hypertension*.
	Less Frequent	Vasculitis, cerebrovascular accident#, vein discolouration, distended vein, flushing*, phlebitis, haematoma (inc. perirenal)*,deep vein thrombosis*, haemorrhage, thrombophlebitis (inc. superficial), circulatory collapse (inc. hypovolaemic shock), poor peripheral circulation*, hyperaemia (inc. ocular)*, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, venous insufficiency, wound haemorrhage
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dyspnoea*, epistaxis, cough*, exertional dyspnoea, upper/lower respiratory tract infection*.
	Less frequent	Hypoxia, pleural effusion, respiratory arrest, pulmonary congestion, asthma, nasal congestion, hoarseness, rhinitis, chest wall pain, sinus pain, productive cough respiratory alkalosis, tachypnoea, wheezing, hyperventilation, orthopnoea, throat tightness,

		pulmonary embolism, pulmonary oedema (inc. acute), pulmonary alveolar haemorrhage#, bronchospasm, chronic obstructive pulmonary disease*, hypoxaemia*, respiratory tract congestion*, pleurisy*, hiccups, dysphonia, respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, haemoptysis, pneumonitis, tachypnoea, pulmonary fibrosis, bronchial disorder*, hypocapnia*, interstitial lung disease, lung infiltration, dry throat, increased upper airway secretion, throat irritation, upper airway cough syndrome .
Gastrointestinal disorders (See section 4.4)	*Frequent*	Vomiting symptoms*, diarrhoea*, nausea, constipation, abdominal pain (inc. gastrointestinal and splenic pain)*, stomatitis*, dyspepsia, loose stools, abdominal distension, mouth ulceration, dry mouth flatulence gastrointestinal haemorrhage (inc. mucosal)*, oropharyngeal pain*, oral disorder*.

	Less frequent	Acute pancreatitis, paralytic ileus, antibiotic associated colitis, colitis (inc. clostridium difficile)*, haematemesis, haemorrhagic diarrhoea, gastrointestinal haemorrhage, rectal haemorrhage, dysphagia, oral pain, retching, eructation, gastrointestinal pain, hiatus hernia, oral mucosal, enteritis*, abdominal discomfort, gastrointestinal motility disorder*, change in bowel habit, spleen pain, oesophagitis, gastritis*, gastro-oesophageal reflux disease*, gingival bleeding gingival hypertrophy, irritable bowel syndrome, pancreatitis (inc. chronic)*, lip swelling*, gastrointestinal obstruction (inc. small intestinal obstruction, ileus)*,oral ulceration*, colitis ischaemic#, gastrointestinal inflammation, gastrointestinal disorder NOS, tongue coated, salivary gland disorder*, peritonitis*, tongue oedema*, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony,

		faecaloma*, gastroinstestinal ulceration and perforation*, megacolon, rectal discharge, oropharyngeal blistering*, lip pain, periodontitis, anal fissure, proctalgia, abnormal faeces
Hepatobiliary disorders (See section 4.4)	*Frequent*	Hepatic enzyme abnormality*
	Less frequent	Hepatitis, hepatic haemorrhage, hepatotoxicity (inc. liver disorder), cholestasis, hepatic failure, hepatomegaly, Budd-chiari syndrome, cytomegalovirus hepatitis, cholelithiasis, hypoproteinaemia.
Skin and subcutaneous tissue disorders	*Frequent*	Rash*, pruritus*, erythema, dry skin, eczema.
	Less frequent	Psoriasis, dermatitis*, night sweats, Erythema multifome, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis#, Steven-Johnson Syndrome, hair disorder*, petechiae, ecchymosis, skin lesion, purpura, skin mass, psoriasis, hyperhidrosis, decubitus ulcer#, 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, contusion, generalised pruritus, macular rash, popular rash, generalised rash, alopecia, skin discolouration, atopic dermatitis, abnormal hair texture, heat rash, pressure sore, skin nodule
Musculoskeletal and connective tissue disorders	*Frequent*	Muscle weakness, musculoskeletal pain*, pain in limb, muscle spasms*, muscle cramps, arthralgia, bone pain, back pain, peripheral swelling, myalgia.
	Less frequent	Muscle twitching or sensation of heaviness, joint swelling, joint stiffness, pain in jaw, arthritis*, myopathies*, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, bone disorder, musculoskeletal and connective tissue infections and inflammations*, synovial cyst, muscle stiffness, buttock pain, swelling
Renal and urinary disorders	*Frequent*	Renal impairment*, dysuria
	Less frequent	Acute renal failure, renal failure chronic, urinary tract infection*,

		oliguria*, haematuria*, proteinuria, urinary retention, micturition disorder*, urinary tract signs and symptoms*, azotaemia, pollakiuria, bladder irritation, renal colic, urinary frequency, loin pain, urinary incontinence, micturition urgency .
Reproductive system and breast disorders	*Less frequent*	Testicular disorder*, erectile dysfunction, vaginal haemorrhage, genital pain*, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration, embryotoxicity, teratogenicity.
Congenital, familial genetic disorders	*Less frequent*	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions	*Frequent*	Fatigue, pyrexia*, asthenia, malaise*, pain*, chills, oedema (inc. peripheral), weakness, chest pressure sensation, groin pain, chest tightness.
	Less frequent	Mucosal disorder*, injection site haemorrhage*, inflammation, injection site phlebitis*, extravasation* tenderness, injection site reaction*, feeling cold, chest discomfort, general physical health deterioration*, face oedema*, chest

		pain, Gait disturbance, catheter related complication*, change in thirst, feeling of body temperature change*, injection site pain*, catheter site pain.
Investigations	*Frequent*	Decreased weight, increased blood lactate dehydrogenase.
	Less frequent	Increased C-reactive protein, increased weight, hyperbilirubinaemia*, protein analyses abnormal*, blood test abnormal*, blood gases abnormal*, electrocardiogram abnormalities (inc. QT prolongation)*, international normalised ratio (INR) abnormal*, gastric pH decreased, platelet aggregation increased, troponin I increased, virus identification and serology*, urine analysis abnormal*, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased blood creatinine, increased blood urea, increased gamma-glutamyltransferase, increased blood

		amylase, abnormal liver function tests, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate.
Injury, poisoning and procedural complications	*Less frequent*	Procedural pain, burns, fall, confusion, transfusion reaction, fractures* rigors*, face injury, joint injury*, burns, laceration, radiation injuries*, post procedural haemorrhage.
Surgical and medical procedures	*Less frequent*	Macrophage activation

NOS= not otherwise specified

*Grouping or more than one MedDRA preferred term

Post-marketing adverse reaction regardless of indication

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found online under SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000

4.9 Overdose

One case of overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported with BOTIGEN 3,5.

Overdosage was associated with acute onset of symptomatic hypotension 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

Category and Class:

A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG01.

Mechanism of action

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

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

Bortezomib is highly selective for the proteasome. At 10 μM concentrations, bortezomib does not inhibit any of a widevariety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and Nuclear Factor kappa B (NF-kB) activation.

Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourogenesis, including cell growth and survival, angiogenesis, cell: cell interactions, and metastasis.
In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth in vivo in many preclinical tumour models, including multiple myeloma.
Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

5.2 Pharmacokinetic properties

Absorption:

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

Distribution:

The mean distribution volume (Vd) of bortezomib ranged from 1 659 to 3 294 litres following single- or repeated-dose intravenous administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues.

The binding of bortezomib to human plasma averaged 83 % over the concentration range 100 – 1 000 mg/mL.

Biotransformation:

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor.

The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination:

The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours.

The pathways of bortezomib elimination have not been characterized in humans.

Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Special Populations

Age, Gender and Race:

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 - 16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (% CV) clearance was 7,79 (25 %) L/hr/m^2, volume of distribution at steady state was 834 (39 %) L/m2, 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.

Renal Impairment:

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

Hepatic impairment

The effect of hepatic impairment (see Table 2 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Mannitol (35 mg per vial)

6.2 Incompatibilities

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

This medicine must be reconstructed with sodium chloride (0.9 %) solution for injection only.

6.3 Shelf life

BOTIGEN 3,5 Powder for solution for injection: 36 months.

Reconstituted product:

32 days when stored at 2–8 °C, in its original vial as well as in polypropylene syringes.

15 days when stored at room temperature (below 25 °C), in its original vial and in polypropylene syringes.

6.4 Special precautions for storage

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

Store at or below 25 °C.

Reconstituted solution

Bortezomib for Injection (3.5 mg/vial) remains stable when reconstituted with 0,9 % Sodium Chloride Injection at concentrations of 1,0 mg/mL and 2,5 mg/mL for a period of 32 days in its original vial as well as in polypropylene syringes when stored at 2–8 °C and protected from light. Similarly, the product is stable for 15 days in its original vial and in polypropylene syringes when stored at room temperature (below 25 °C) and protected from light. Protection from light is essential to maintain the claimed stability during these storage periods.

6.5 Nature and contents of container

10 ml tubular colourless Type 1 glass vial with a grey bromobutyl rubber stopper, sealed with a light green flip off aluminium seal.

The vial is contained in a transparent blister pack consisting of a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal

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

Aseptic technique must be strictly observed throughout the handling of BOTIGEN 3,5, since it contains no preservative.

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

BOTIGEN 3,5 is for intravenous or subcutaneous use.

BOTIGEN 3,5 should not be administered intrathecally.

Instructions for reconstitution

BOTIGEN 3,5 must be reconstituted by a healthcare professional.

Intravenous injection

Each 10 mL vial of BOTIGEN 3,5 must be carefully reconstituted with 3,5 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper.

Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 1 mg bortezomib.

The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration.

If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Each 10 mL vial of BOTIGEN 3,5 must be carefully reconstituted with 1.4 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper.

Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each ml solution contains 2,5 mg bortezomib.

The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration.

If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal

BOTIGEN 3,5 is for single use only.

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

7. HOLDER OF CERTIFICATES OF REGISTRATION

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8. REGISTRATION NUMBER

51/26/0163

9. DATE OF FIRST AUTHORISATION

Date of registration: 28 July 2020

10. DATE OF REVISION OF THE TEXT

27 January 2025