AUSTRALIAN PRODUCT INFORMATION

BORTEZOMIB EVER PHARMA ®

(bortezomib) solution for injection

1. NAME OF THE MEDICINE

Bortezomib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BORTEZOMIB EVER PHARMA (bortezomib) is an antineoplastic agent for intravenous injection (IV) or subcutaneous (SC) use only. Each 1 mL vial contains 1.0 mL solution for injection which contains 2.5 mg bortezomib (as a mannitol boronic ester).Also contains 25 mg mannitol

Each 1.4 mL vial contains 1.4 mL solution for injection which contains 3.5 mg bortezomib (as a mannitol boronic ester) Also contains 35 mg mannitol.

For subcutaneous injection, no dilution is necessary.
1 mL of solution for subcutaneous injection contains 2.5 mg bortezomib.

For intravenous injection, dilution is necessary.
1 mL of diluted solution for intravenous injection contains 1 mg bortezomib.

Excipient with known effect:
Each mL of concentrate contains less than 1 mmol (approximately 3.5 mg) sodium.

For a full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for injection. Colourless to light yellow solution with a pH-value of 4.0 – 5.5.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)- 1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl] boronic acid.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

BORTEZOMIB EVER PHARMA, in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.

BORTEZOMIB EVER PHARMA, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.

BORTEZOMIB EVER PHARMA is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

BORTEZOMIB EVER PHARMA in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma.

4.2. DOSE AND METHOD OF ADMINISTRATION

The product is supplied sterile and is for use in one patient only.

BORTEZOMIB EVER PHARMA may be administered:

- Intravenously (at a concentration of 1 mg/mL) as a 3-5 second bolus injection or
- Subcutaneously (at a concentration of 2.5 mg/mL)

Because each route of administration has a different concentration, caution should be used when calculating the volume to be administered.
BORTEZOMIB EVER PHARMA IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY.

Intrathecal administration has resulted in death.

Recommended Dosage

Previously Untreated Multiple Myeloma - Transplant Eligible

1. BORTEZOMIB EVER PHARMA plus thalidomide-dexamethasone

During the induction stage, BORTEZOMIB EVER PHARMA (bortezomib) is administered twice weekly in combination with thalidomide-dexamethasone for three 3-week treatment cycles. The treatment regimen is shown in **Table 1**.

Table 1: Recommended dosage regimen for BORTEZOMIB when used in combination with thalidomide and dexamethasone

Induction Therapy: Twice weekly BORTEZOMIB (3 cycles)

Week	1				2					3
B (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	--	--	--	Day 11	--
t (100 mg)-Cycle 1	Day 1-7				Day 8-14					--
t (200 mg)-Cycle 2-3	Day 1-7				Day 8-14					Day 15-21
d (40 mg)	Day 1	Day 2	--	Day 4	Day 5	Day 8	Day 9	--	Day 11	Day 12	--

B = BORTEZOMIB; t = thalidomide; d = dexamethasone

2. BORTEZOMIB EVER PHARMA plus dexamethasone

BORTEZOMIB EVER PHARMA (bortezomib) is administered as an IV injection in combination with oral dexamethasone for four 3-week treatment cycles as shown in **Table 2**.

Table 2: Recommended dosage regimen for BORTEZOMIB when used in combination with dexamethasone

Week	1		2				3
B (1.3 mg/m^2)	Day 1	Day 4	Day 8	--	Day 11	--	--
d (40 mg)-All Cycles	Day 1-4		--				--
d (40 mg)-Cycle 1-2	--		Day 9-12				--

B = BORTEZOMIB; d = dexamethasone

Previously Untreated Multiple Myeloma - Non-Transplant Eligible

BORTEZOMIB EVER PHARMA (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in **Table 3**. In Cycles 1-4, BORTEZOMIB EVER PHARMA is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, BORTEZOMIB EVER PHARMA is administered once weekly (days 1, 8, 22 and 29).

Table 3: Recommended Dosage Regimen for BORTEZOMIB when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma

Twice Weekly BORTEZOMIB (Cycles 1-4)

Week	1				2		3	4		5		6
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

Once Weekly BORTEZOMIB (Cycles 5-9)

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 = BORTEZOMIB; m = melphalan, p=prednisone

Dose Management Guidelines

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

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥70 x 10^9/L and the ANC should be ≥ 1.0 x 10^9/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 4: Dose Modifications during Subsequent Cycles:	
Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.75 \times 10^9$/L on a BORTEZOMIB dosing day (other than day 1)	BORTEZOMIB dose should be withheld
If several BORTEZOMIB doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	BORTEZOMIB 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	BORTEZOMIB therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB 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 BORTEZOMIB related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB A as outlined in **Table 5**.

For additional information concerning melphalan and prednisone, see manufacturer's Product Information documents.

Table 5: Recommended Dose Modification for BORTEZOMIB -related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy.	
Severity of Peripheral Neuropathy Signs and Symptoms*	**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)**)	Reduce BORTEZOMIB to 1.0 mg/m^2 OR Change BORTEZOMIB treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)***	Withhold BORTEZOMIB therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue BORTEZOMIB
* Grading based on NCI Common Toxicity Criteria CTCAE v 4.0 ** *Instrumental ADL:* refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc; *** *Self care ADL:* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

Relapsed / Refractory Multiple Myeloma

Recommended Dose

The recommended dose of BORTEZOMIB EVER PHARMA is 1.3 mg/m^2/dose 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. At least 72 hours should elapse between consecutive doses of BORTEZOMIB EVER PHARMA.

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

For extended therapy of more than 8 cycles, BORTEZOMIB EVER PHARMA may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22) followed by a 13-day rest period (days 23 to 35) (see **Clinical trials** for a summary of dose administration during clinical trials).

Dose Modification and Reinitiation of Therapy

BORTEZOMIB therapy should be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities excluding neuropathy as discussed above (see **section 4.4 Special warnings and precautions for use**). Once the symptoms of the toxicity have resolved, BORTEZOMIB therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). **Table 5** contains the recommended dose modification for the management of patients who experience BORTEZOMIB-related neuropathic pain and/or peripheral sensory neuropathy. Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy should be treated with BORTEZOMIB only after careful risk/benefit assessment.

Previously Untreated Mantle Cell Lymphoma

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

BORTEZOMIB EVER PHARMA (bortezomib) for injection is administered at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10 day rest period on days 12-21. This 3 week period is considered a treatment cycle. Six BORTEZOMIB cycles are recommended, although for patients with a response first documented at cycle 6, two additional BORTEZOMIB cycles may be given. At least 72 hours should elapse between consecutive doses of BORTEZOMIB.

The following medicinal products are administered on Day 1 of each BORTEZOMIB 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 initiating a new cycle of therapy:

- 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
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

BORTEZOMIB treatment must be withheld at the onset of any ≥ Grade 3 BORTEZOMIB-related non haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also **section 4.4 Special warnings and precautions for use**). For dose adjustments, see **Table 6** below. Colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Platelet transfusion for the treatment of thrombocytopenia may be considered.

Table 6: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Toxicity	Posology modification or delay
Hematological toxicity • ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10×10^9/L	BORTEZOMIB therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0.75×10^9/L and a platelet count ≥ 25×10^9/L. • If, after BORTEZOMIB has been held, the toxicity does not resolve, as defined above, then BORTEZOMIB must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 0.75×10^9/L and a platelet count ≥ 25×10^9/L, BORTEZOMIB may be reinitiated at a dose reduced by one dose level (from1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
• If platelet counts < 25×10^9/L. or ANC < 0.75×10^9/L on a BORTEZOMIB dosing day (other than Day 1 of each cycle)	BORTEZOMIB dose should be withheld
Grade ≥ 3 non-hematological toxicities considered to be related to BORTEZOMIB	BORTEZOMIB therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BORTEZOMIB 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 BORTEZOMIB -related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB as outlined in **Table 5**.

In addition, when BORTEZOMIB is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Product Information documents.

Method of administration

Intravenous injection (IV)

BORTEZOMIB EVER PHARMA 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.

Subcutaneous injection (SC)

The 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 BORTEZOMIB EVER PHARMA injection subcutaneously, a less concentrated BORTEZOMIB solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously or change to IV injection.

When BORTEZOMIB is given in combination with other medicinal products, refer to the Product Information for these products for instructions for administration.

Instructions for Use and Handling and Disposal

Administration Precautions:

BORTEZOMIB EVER PHARMA is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of BORTEZOMIB was not associated with tissue damage.

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

There have been fatal cases of inadvertent intrathecal administration of BORTEZOMIB. BORTEZOMIB EVER PHARMA is for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB EVER PHARMA INTRATHECALLY**.

Instructions for preparation and administration

BORTEZOMIB EVER PHARMA must be prepared by a healthcare professional.

Intravenous injection

Each 2.5 mg/1 mL vial of **BORTEZOMIB EVER PHARMA** must be carefully diluted with 1.5 mL sodium chloride 9 mg/mL (0.9 %) solution for injection for an intravenous injection, *by using a syringe of the appropriate size, without removing the vial stopper*.

OR

Each 3.5 mg/1.4 mL vial of **BORTEZOMIB EVER PHARMA** must be carefully diluted with 2.1 mL sodium chloride 9 mg/mL (0.9 %) solution for injection for an intravenous injection, *by using a syringe of the appropriate size, without removing the vial stopper*.

After dilution, each mL solution contains 1 mg bortezomib. The diluted solution is clear and colourless to light yellow and practically free from visible particles, with a final pH of 4 to 7. The diluted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the diluted solution must be discarded.

Subcutaneous injection

Each vial of **BORTEZOMIB EVER PHARMA** is ready to use for a subcutaneous injection. Each mL solution contains 2.5 mg bortezomib. The solution is clear and colourless to light yellow with pH of 4.0 to 5.5. The solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the solution must be discarded.

Disposal

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. If any discolouration or particulate matter is observed, the product should not be used.

Procedure for proper disposal:

BORTEZOMIB EVER PHARMA is for single use in one patient on one occasion only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

Dosage adjustment in:

Renal insufficiency

Based on the data from a small study, the pharmacokinetics of BORTEZOMIB are not influenced by mild (CrCL = 40-59 mL/min/1.73 m^2, n=10) or moderate (CrCL = 20-39 mL/min/1.73 m^2, n=9) renal impairment. Therefore, dosing adjustments of BORTEZOMIB are not necessary for these patients. The effect of severe renal impairment (CrCl < 20mL/min/1.73m^2) has not been determined. Since dialysis may reduce BORTEZOMIB concentrations, the drug should be administered after the dialysis procedure (see **section 5.2 Pharmacokinetic properties)**.

Hepatic insufficiency

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended BORTEZOMIB dose. Patients with moderate or severe hepatic impairment should be started on BORTEZOMIB 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 7**).

Table 7: Recommended Starting Dose Modification for BORTEZOMIB in Patients with Hepatic Impairment

	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose**
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x–1.5x ULN	Any	None
Moderate	> 1.5x–3x ULN	Any	Reduce BORTEZOMIB 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	> 3x ULN	Any	

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

4.3. CONTRAINDICATIONS

BORTEZOMIB EVER PHARMA is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Overall treatment with BORTEZOMIB EVER PHARMA must be done under the supervision of a physician, however administration of the drug product may be done by a healthcare professional experienced in the administration of oncology medications.

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

BORTEZOMIB EVER PHARMA is for intravenous or subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB EVER PHARMA INTRATHECALLY**.

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

Peripheral neuropathy

BORTEZOMIB treatment causes a peripheral neuropathy (PN) 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 burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening (including ≥ Grade 3) during treatment with BORTEZOMIB. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperaesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

In the Phase 3 study comparing BORTEZOMIB IV vs. SC the incidence of Grade ≥2 peripheral neuropathy events was 24% for SC and 41% for IV (p=0.0124). Grade ≥3 peripheral neuropathy occurred in 6% of subjects in the SC treatment group, compared with 16% in the IV treatment group (p=0.0264). Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting BORTEZOMIB subcutaneously.

Patients experiencing new or worsening peripheral neuropathy may require a change in dose, schedule or route of administration to SC (see **section 4.2 Dose and method of administration**).

Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the phase III multiple myeloma study of BORTEZOMIB IV vs. dexamethasone. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the phase II studies (see **section 4.8 Adverse effects (undesirable effects**)).

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.

Hypotension

Patients developing orthostatic hypotension on BORTEZOMIB did not have evidence of orthostatic hypotension prior to treatment with BORTEZOMIB. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of BORTEZOMIB.

In phase II and III studies, the incidence of hypotension (postural, orthostatic and hypotension not otherwise specified) was 11% to 12%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope receiving medications known to be associated with hypotension and with patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids and/or sympathomimetics (see **section 4.8 Adverse effects (undesirable effects)**).

Cardiac disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or an existing heart disease should be closely monitored. In the phase III study of BORTEZOMIB IV vs. dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13%, respectively. The incidence of heart failure events (acute pulmonary oedema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary oedema) was similar in the BORTEZOMIB and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving BORTEZOMIB. 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, two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion with daunorubicin and BORTEZOMIB for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy.

Thrombotic Microangiopathy

There have been cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) reported in patients who received proteasome inhibitors. Some of these events have been fatal. Patients receiving BORTEZOMIB should be monitored for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop BORTEZOMIB and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, BORTEZOMIB can be reinitiated. The safety of reinitiating BORTEZOMIB therapy in patients previously experiencing TTP/HUS is not known.

Posterior reversible encephalopathy syndrome (PRES)

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

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.

Amyloidosis

A phase 1/2 single-agent BORTEZOMIB dose-escalation study was conducted in patients with previously treated light-chain Amyloidosis. At planned interim analysis, no new safety concerns were observed and no evidence of target organ damage was found during the study.

Laboratory tests

Complete blood counts (CBC) should be frequently monitored throughout treatment with BORTEZOMIB.

Thrombocytopenia/neutropenia

BORTEZOMIB treatment is associated with thrombocytopenia and neutropenia (see **section 4.8 Adverse effects (undesirable effects)**). Platelet counts were lowest at Day 11 of each cycle of BORTEZOMIB treatment and typically recovered to baseline by the next cycle. The pattern of platelet count decrease and recovery remained 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 BORTEZOMIB. BORTEZOMIB therapy should be held when the platelet count is <25,000/μL (see **sections 4.2 Dose and method of administration** and **4.8 Adverse effects (undesirable effects)**). There have been reports of gastrointestinal and intracerebral hemorrhage in association with BORTEZOMIB. Transfusion and supportive care may be considered at the discretion of the physician.

In the single-agent 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 8** for the phase III study. The incidence of significant bleeding events (≥ Grade 3) was similar on both the BORTEZOMIB (4%) and dexamethasone (5%) arms.

Table 8: The Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the APEX study of BORTEZOMIB IV vs. dexamethasone

Pre-treatment Platelet Count*	Number of Patients (N= 331)**	Number (%) of Patients with Platelet Count <10,000/μL	Number (%) of Patients with Platelet Count 10,000/μL – 25,000μL
≥ 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%)

* A baseline platelet count of 50,000/μL was required for study eligibility.
** Data for one patient was missing at baseline
Thrombocytopenia was reported in 43% of patients in the phase II studies.

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% versus 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 was 52% in the R-

CHOP arm. The incidence of febrile neutropenia (≥ Grade 4) was 5% in the BR-CAP arm and was 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 adverse events

BORTEZOMIB treatment can cause nausea, diarrhoea, constipation and vomiting (see **section 4.8 Adverse effects (undesirable effects)**) sometimes requiring use of antiemetics and antidiarrhoeals. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving BORTEZOMIB therapy may experience vomiting and/or diarrhoea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Tumour lysis syndrome

Because BORTEZOMIB is a cytotoxic agent and can rapidly kill malignant cells the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB (see **section 4.8 Adverse effects (undesirable effects**)**).**

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the B+M+P arm. The incidence of herpes zoster among patients in the B+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle Cell Lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the BR-CAP arm. The incidence of herpes zoster among patients in the BR-CAP arm was 4.6% for patients not administered antiviral prophylaxis compared to 0.8% for patients administered antiviral prophylaxis.

Hepatitis B virus (HBV) reactivation and infection

When rituximab is used in combination with BORTEZOMIB, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with BORTEZOMIB. Antiviral prophylaxis should be considered. Refer to the local Product Information of rituximab for more information.

Hepatic events

Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of BORTEZOMIB. There is limited re-challenge information in these patients.

Use in hepatic impairment

Patients with moderate and severe hepatic impairment should be treated with caution at reduced

starting doses of BORTEZOMIB and closely monitored for toxicities. The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 51 cancer patients with varying degrees of hepatic impairment treated bortezomib doses ranging from 0.5 to 1.3 mg/m^2 (see **Table 7** for definition of hepatic impairment). When compared to patients with normal hepatic function, mild hepatic impairment did not alter bortezomib dose- normalised AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate to severe hepatic impairment.

Use in renal impairment

The incidence of serious undesirable effects may increase in patients with renal impairment compared to patients with normal renal function. Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely. The safety of bortezomib in patients with severe renal impairment (CrCl < 20mL/min/1.73m^2) has not been established. The effect of dialysis on bortezomib plasma concentrations has also not been determined. However, since dialysis may reduce bortezomib concentrations, the drug should be administered after the dialysis procedure.

Use in MCL patients eligible for autologous stem cell transplantation

The pivotal study in previously untreated MCL patients mainly studied patients ineligible for autologous stem cell transplantation, and evidence of efficacy and safety in patients eligible for transplantation is more limited. In particular, there are no data directly informing about the use of BR-CAP as an induction regimen in previously untreated MCL patients who have subsequently received a transplant**.**

Use in the elderly

No data available

Paediatric use

The safety and effectiveness of BORTEZOMIB in children has not been established.

Effects on laboratory tests

None known.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6, and 3A4. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes. 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.

A drug-drug interaction study assessing the effect of ketoconazole (a potent CYP3A4 inhibitor) on the pharmacokinetics of IV BORTEZOMIB showed a bortezomib AUC mean increase of 35%, based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole (a potent inhibitor of CYP2C19) on the pharmacokinetics of IV BORTEZOMIB there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of BORTEZOMIB showed a mean bortezomib AUC reduction of 45%

based on data from 6 patients. The concomitant use of BORTEZOMIB with strong CYP3A4 inducers is not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

Patients who are concomitantly receiving BORTEZOMIB and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy.

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic agents receiving BORTEZOMIB treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

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

Effects on fertility

Fertility studies with bortezomib were not performed but degenerative changes seen in the testes and ovary in a rat general toxicity study suggest that BORTEZOMIB may affect male and female fertility.

Use in pregnancy Category C

Women of child bearing potential should avoid becoming pregnant while being treated with BORTEZOMIB. The placental transfer of bortezomib is unknown, but any occurrence may disrupt cycling in the developing foetus, although teratogenicity was not observed in rats and rabbits at maximum tolerated doses.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (approximately 0.5 mg/m^2/day) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area and calculated on a single-dose basis. Increased post-implantation loss and reduced foetal weights were seen in rabbits at the highest dose tested, which was a maternally toxic dose. Litter values were unaffected by a non-maternotoxic dose (approximately 0.3 mg/m^2/day).

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If BORTEZOMIB is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus.

Patients should be advised to use effective contraceptive measures to prevent pregnancy.

Use in lactation

It is not known whether bortezomib or its metabolites are excreted in animal or human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-fed infants from BORTEZOMIB, women should be advised against breast-feeding while being treated with BORTEZOMIB.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

BORTEZOMIB may cause tiredness, dizziness, fainting or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of Clinical Trials of BORTEZOMIB IV in patients with previously untreated multiple myeloma:

Results from the GIMEMA and IFM2005 studies

The following table describes the safety data from the GIMEMA and IFM2005 studies in patients with previously untreated multiple myeloma who were eligible for autologous stem cell transplantation, and received BORTEZOMIB IV (1.3 mg/m^2) in combination with thalidomide (100 mg, then 200 mg) and dexamethasone (40 mg) in the GIMEMA study, or dexamethasone (40 mg) in the IFM2005 study.

Table 9: Adverse events (Grade III/IV) following induction in randomised, controlled studies GIMEMA and IFM2005

Adverse event, n (%)	**GIMEMA**		**IFM2005**	
	BTD n=236	TD n=238	BD n=239	VAD n=239
Any adverse event	nr	nr	231 (96.7)*	219 (91.6)*
Any serious adverse event	31 (13.1)	30 (12.6)	65 (27.2)	81 (33.9)
Any grade 3 or 4 adverse event	132 (55.9)	79 (33.1)	112 (46.9)	110 (46.0)
Any grade 3 or 4 non-haematologic adverse event	120 (50.8)	73 (30.6)	nr	nr
Skin rash	24 (10.1)	4 (1.6)	nr	nr
Peripheral neuropathy	23 (9.7)	5 (2.1)	17 (7.1)	5 (2.1)
Deep vein thrombosis	8 (3.3)	12 (5.0)	nr	nr
Constipation	10 (4.2)	7 (2.9)	nr	nr
Infections	nr	nr	21 (8.8)	29 (12.1)
Infections excluding herpes zoster	7 (2.9)	11 (4.6)	nr	nr
Herpes zoster (all grades)	nr	nr	22 (9.2)	5 (2.1)
Gastrointestinal events (excluding constipation where individually reported)	5 (2.1)	1 (0.4)	nr	nr
Cardiac toxicity	5 (2.1)	5 (2.1)	nr	nr
Liver toxicity	4 (1.6)	7 (2.9)	nr	nr
Fatigue (all grades)	nr	nr	68 (28.5)	50 (20.9)
Oedema (all grades)	25 (11)	13 (5)		
Any grade 3 or 4 haematologic adverse event	nr	nr	nr	nr
Anaemia	nr	nr	10 (4.2)*	21 (8.8)*
Neutropaenia	nr	nr	12 (5.0)*	24 (10.0)*
Thrombocytopenia	nr	nr	7 (2.9)	3 (1.3)
Thrombosis	nr	nr	4 (1.7)*	13 (5.4)*
Discontinued during or after induction therapy	13 (5.5)	26 (10.9)	44 (18.4)	32 (13.4)
Adverse event leading to death	1 (0.4)	0 (0)	0 (0)*	7 (2.9)*

* $p < 0.05$ for comparison of AE rate between BD and VADBTD: BORTEZOMIB -thalidomide-dexamethasone; TD: thalidomide-dexamethasone; BD: BORTEZOMIB -dexamethasone; VAD: vincristine-doxorubicine-dexamethasone.

During consolidation therapy of the GIMEMA study, grade 3-4 adverse events were similar to those reported during induction, although rates were much lower. Notably, the rate of grade 3-4 peripheral neuropathy was 1.2% with BTD consolidation compared to 0% with TD consolidation.

Results from the VISTA study

The following table describes safety data from the VISTA study in 340 patients with previously untreated multiple myeloma who received BORTEZOMIB IV (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2).

Table 10: Treatment Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with BORTEZOMIB IV in combination with melphalan and prednisone

	---------- BMP ----------			---------- MP ----------		
	(n=340)			(n=337)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System Disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anaemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhoea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥4	n (%)	3	≥4
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal Pain Upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral Neuropathy	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paraesthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0

	---------- BMP ---------- (n=340)			---------- MP ---------- (n=337)		
	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB. In the VISTA study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with BMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administrated to 26% of the patients in the BMP arm. The incidence of herpes zoster among patients in the BMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis. Similar results were observed during the IFM2005 study; herpes zoster was more common in patients treated with BORTEZOMIB-based regimen compared to control regimen (9.2% vs. 2.1%). During consolidation, the GIMEMA study reported similar rates (0.6%) of grade 3-4 incidences of herpes zoster between the two study arms (*p*=1.0000).

Summary of Clinical Trials of BORTEZOMIB IV in patients with relapsed/refractory multiple myeloma:

The adverse events most commonly reported, regardless of causality, in the APEX study in relapsed / refractory multiple myeloma patients (see **Clinical trials**) are presented in **Table 11**. All adverse events occurring at ≥10% are included.

Table 11: Most Commonly Reported (≥10% in BORTEZOMIB arm) Adverse Events in the APEX Study using the 1.3 mg/m^2 dose (N=663)

	BORTEZOMIB (N=331)			**Dexamethasone (N=332)**		
	All Events %	**Grade 3 %**	**Grade 4 %**	**All Events %**	**Grade 3 %**	**Grade 4 %**
Adverse Event	**100**	**61**	**14**	**98**	**44**	**16**
Body as a Whole-General Disorders						
Asthenic conditions (fatigue, malaise, weakness)	61	12	<1	45	6	0
Pyrexia	35	2	0	16	1	<1
Rigors	11	0	0	2	0	0
Oedema lower limb	11	0	0	13	<1	0
Gastro-Intestinal System Disorders						
Diarrhoea	57	7	0	21	2	0
Nausea	57	2	0	14	0	0
Constipation	42	2	0	15	1	0
Vomiting	35	3	0	6	1	0
Abdominal pain	16	2	0	4	<1	0

	BORTEZOMIB (N=331)			Dexamethasone (N=332)		
	All Events %	**Grade 3 %**	**Grade 4 %**	**All Events %**	**Grade 3 %**	**Grade 4 %**
Central & Peripheral Nervous System Disorders						
Peripheral Neuropathy*	36	7	<1	9	<1	<1
Paraesthesia and dysaesthesia	27	2	0	11	<1	0
Headache	26	<1	0	13	<1	0
Dizziness (excluding vertigo)	14	<1	0	10	0	0
Blood and lymphatic system disorders						
Thrombocytopenia	35	26	4	11	5	1
Anemia	26	9	<1	22	10	<1
Neutropenia	19	12	2	2	1	0
Psychiatric disorders						
General	35	3	<1	49	5	1
Insomnia	18	<1	0	27	2	0
Metabolic and Nutritional Disorders						
Appetite decreased and anorexia	34	3	0	9	<1	0
Respiratory System disorders						
Cough	21	<1	0	11	<1	0
Dyspnoea	20	5	<1	17	3	<1
Skin and subcutaneous tissue disorders						
Rash	18	1	0	6	0	0
Infections and infestations						
Lower respiratory/lung infections	15	4	<1	21	5	<1
Nasopharyngitis	14	<1	0	7	0	0
Herpes zoster	13	2	0	5	1	<1
Musculoskeletal and connective tissue disorders						
Bone pain	16	4	0	15	3	0
Pain in limb	15	2	0	7	<1	0
Back pain	14	3	0	10	1	0
Arthralgia	14	<1	0	11	2	0
Muscle cramps	12	0	0	15	<1	0
Myalgia	12	<1	0	5	<1	0

*Peripheral neuropathy includes all terms under peripheral neuropathy not elsewhere classified (NEC), (Peripheral neuropathy not otherwise specified (NOS), peripheral neuropathy aggravated, peripheral sensory neuropathy and peripheral motor neuropathy and neuropathy NOS).

Summary of Clinical Trials of BORTEZOMIB IV vs. SC in patients with relapsed multiple myeloma:

The safety and efficacy of BORTEZOMIB SC were evaluated in one Phase III study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of BORTEZOMIB IV vs. SC in 222 patients with relapsed multiple myeloma.

Table 12: Incidence of BORTEZOMIB Adverse Drug Reactions reported in ≥ 10% of patients in the Phase 3 Relapsed Multiple Myeloma Study comparing BORTEZOMIB IV and SC

	---------- IV ----------			---------- SC ----------		
MedDRA System Organ Class	(N=74) Total	-- Toxicity Grade, n (%) --		(N=147) Total	-- Toxicity Grade, n (%) --	
Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	26 (35)	6 (8)	0	53 (36)	14 (10)	4 (3)
Leukopenia	16 (22)	4 (5)	1 (1)	29 (20)	9 (6)	0
Neutropenia	20 (27)	10 (14)	3 (4)	42 (29)	22 (15)	4 (3)
Thrombocytopenia	27 (36)	8 (11)	6 (8)	52 (35)	12 (8)	7 (5)
Gastrointestinal disorders						
Abdominal pain	8 (11)	0	0	5 (3)	1 (1)	0
Abdominal pain upper	8 (11)	0	0	3 (2)	0	0
Constipation	11 (15)	1 (1)	0	21 (14)	1 (1)	0
Diarrhoea	27 (36)	3 (4)	1 (1)	35 (24)	2 (1)	1 (1)
Nausea	14 (19)	0	0	27 (18)	0	0
Vomiting	12 (16)	0	1 (1)	17 (12)	3 (2)	0
General disorders and administration site conditions						
Asthenia	14 (19)	4 (5)	0	23 (16)	3 (2)	0
Fatigue	15 (20)	3 (4)	0	17 (12)	3 (2)	0
Pyrexia	12 (16)	0	0	28 (19)	0	0
Infections and infestations						
Herpes zoster	7 (9)	1 (1)	0	16 (11)	2 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	7 (9)	0	0	14 (10)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	8 (11)	2 (3)	0	8 (5)	1 (1)	0
Nervous system disorders						
Headache	8 (11)	0	0	5 (3)	0	0
Neuralgia	17 (23)	7 (9)	0	35 (24)	5 (3)	0
Peripheral sensory neuropathy	36 (49)	10 (14)	1 (1)	51 (35)	5 (3)	0
Psychiatric disorders						
Insomnia	8 (11)	0	0	18 (12)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	9 (12)	2 (3)	0	11 (7)	2 (1)	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.

Percentages of toxicity grade sub-groups calculated with the number of subjects in each group as denominator.

Although, in general safety data were similar for the IV and SC treatment groups, the following table highlights differences larger than 10% in the overall incidence of adverse drug reactions between the two treatment arms.

Table 13: Incidence of Adverse Drug Reactions with >10% Difference in Overall Incidence between Treatment Arms in the Phase 3 Relapsed Multiple Myeloma Study comparing BORTEZOMIB IV and SC, by Toxicity Grade and Discontinuation

	---------- IV ---------- (N=74)			---------- SC ---------- (N=147)		
MedDRA System Organ Class	----- Category, n (%) -----			----- Category, n (%) -----		
MedDRA High Level Term	TEAE	G ≥ 3	Disc	TEAE	G ≥ 3	Disc
All subjects with TEAE	73 (99)	52 (70)	20 (27)	140 (95)	84 (57)	33 (22)
Gastrointestinal disorders						
Diarrhoea (excl infective)	27 (36)	4 (5)	1 (1)	35 (24)	3 (2)	1 (1)
Gastrointestinal and abdominal pains (excl oral and throat)	14 (19)	0	0	9 (6)	1 (1)	0
General disorders and administration site conditions						
Asthenic conditions	29 (39)	7 (9)	1 (1)	40 (27)	6 (4)	2 (1)
Infections and infestations						
Upper respiratory tract infections	19 (26)	2 (3)	0	20 (14)	0	0
Nervous system disorders						
Peripheral neuropathies NEC	39 (53)	12 (16)	10 (14)	56 (38)	9 (6)	9 (6)

G ≥ 3 = Toxicity Grade greater than equal to 3
Disc = Discontinuation of any study drug.

Patients who received BORTEZOMIB subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment emergent adverse drug reactions that were grade 3 or higher in toxicity (57% vs 70% respectively; *p*-value is 0.0784), and a 5% lower incidence of discontinuation of BORTEZOMIB (22% vs 27%; *p*-value is 0.5052). The overall incidence of diarrhoea (24% for the SC arm vs 36% for the IV arm; *p*-value is 0.0572), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm; *p*-value is 0.0049), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm; *p*-value is 0.0903) and peripheral neuropathy NEC (38% SC arm vs 53% IV arm; *p*-value is 0.0444) were 12%-15% lower in the subcutaneous group than the intravenous group. In addition, the incidence of peripheral neuropathies that were grade 3 or higher in toxicity was 10 % lower (6% for SC vs 16% for IV; *p*-value is 0.0264), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (14%); *p*-value is 0.0771.

58 percent of patients (85/147) developed a reaction at the site of subcutaneous injection. Only 2 (1.4%) subjects were reported as having severe reactions. These severe local reactions were 1 case of pruritus and 1 case of redness. These reactions seldom led to dose modifications and all resolved in a median of 6 days (BORTEZOMIB treatment modification based on local reactions was needed in 2 subjects (1 treatment discontinuation; 1 drug withholding and reduction in study drug concentration from 2.5 mg/mL to 1 mg/mL).

Serious Adverse Events (SAEs)

In the APEX study, 44% of patients from the BORTEZOMIB treatment arm experienced a SAE

during the study, as did 43% of dexamethasone-treated patients. The most commonly reported SAEs in the BORTEZOMIB treatment arm were pyrexia (6%), diarrhoea (5%), dysponea and pneumonia (4%) and vomiting (3%). In the dexamethasone group, the most common SAEs were pneumonia (7%), pyrexia (4%) and hyperglycaemia (3%). Twenty five percent (25%) and 18% of BORTEZOMIB and dexamethasone patients respectively were discontinued from treatment due to adverse events assessed as drug related by the investigators. The most common for BORTEZOMIB discontinuation was peripheral neuropathy (8%) and for dexamethasone was psychotic disorder and hyperglycaemia (2% each).

In the APEX study, 4 deaths were considered to be BORTEZOMIB-related: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four (4) deaths were considered dexamethasone–related: 2 cases of sepsis, 1 case of bacterial meningitis and 1 case of sudden death at home. In the phase II studies 2 deaths were reported and considered by the investigator to be possibly related to BORTEZOMIB: 1 case of cardiopulmonary arrest and 1 case of respiratory failure.

Adverse reactions

The following adverse reactions were considered to have at least a possible or probable causal relationship to BORTEZOMIB by the investigators during 5 non-comparative phase II studies and 1 comparative phase III trial (APEX) in 663 patients with relapsed or refractory multiple myeloma, of whom 331 received BORTEZOMIB as single agent. The safety database comprises data from patients with multiple myeloma or B-cell lymphocytic leukaemia. Patients were treated with BORTEZOMIB as a single agent, or in combination with dexamethasone.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Table 14. Adverse Drug Reactions listed by system organ class and frequency

Infections and infestations	
Common:	herpes zoster, pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex.
Uncommon:	candidal infection, gastroenteritis, upper and lower respiratory tract infection, infection, influenza, fungal infection, sepsis, urinary tract infection, catheter related infection, haemophilus infection, pneumonia pneumococcal, post herpetic neuralgia, bacteraemia, blepharitis, bronchopneumonia, cytomegalovirus infection, infectious mononucleosis, varicella, oral candidiasis, pleural infection.
Blood and lymphatic system disorders	
Very Common:	thrombocytopenia (see **section 4.4 Special warnings and precautions for use**), anaemia, neutropenia.
Common:	leukopenia, lymphopenia.
Uncommon:	lymphadenopathy, febrile neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenic purpura.
Immune system disorders	
Uncommon:	hypersensitivity, immunocomplex mediated hypersensitivity.

Metabolism and nutritional disorders	
Very Common:	appetite decreased.
Common:	dehydration, hyperglycaemia, hypokalaemia.
Uncommon:	hypercalcaemia, hyperkalaemia, hyperuricaemia, hyponatraemia, hypernatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, hypoglycaemia, appetite increased, cachexia, vitamin B12 deficiency, tumour lysis syndrome (see **section 4.4 Special warnings and precautions for use**).
Endocrine disorders	
Uncommon:	Inappropriate antidiuretic hormone (ADH) secretion.
Psychiatric disorders	
Common:	insomnia, anxiety, confusion, depression.
Uncommon:	agitation, delirium, restlessness, mood swings, mental status changes, sleep disorder, irritability, hallucinations, abnormal dreams.
Nervous system disorders	
Very Common:	peripheral neuropathy, peripheral sensory neuropathy (see **section 4.4 Special warnings and precautions for use**), headache, paraesthesia.
Common:	dizziness (excluding vertigo), dysgeusia, peripheral neuropathy aggravated, polyneuropathy, dysaesthesia, hypoaesthesia, tremor.
Uncommon:	convulsions, syncope, disturbance in attention, increased activity, ageusia, somnolence, migraine, peripheral motor neuropathy, jerky movements, dizziness postural, sciatica, cognitive disorder, mononeuropathy, paresis, restless leg syndrome, speech disorder, intracranial haemorrhage, paraplegia, subarachnoid haemorrhage.
Eye disorders	
Common:	vision blurred (see **section 4.4 Special warnings and precautions for use**), eye pain.
Uncommon:	dry eye, conjunctivitis, eye discharge, vision abnormal, eye haemorrhage, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.
Ear and labyrinth disorders	
Common:	vertigo.
Uncommon:	tinnitus, deafness, hypoacusis, hearing impaired.

Cardiac disorders	
Uncommon:	Development or exacerbation of congestive heart failure (see **section 4.4 Special warnings and precautions for use**), cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, cardiac arrest, cardiogenic shock, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations, sinus arrest, atrioventricular block complete, angina pectoris, angina unstable, myocardial infarction.
Rare:	New onset of decreased left ventricular ejection fraction.
Vascular disorders	
Common:	hypotension, orthostatic and postural hypotension (see **section 4.4 Special warnings and precautions for use**), phlebitis, haematoma, hypertension.
Uncommon:	flushing, petechiae, hot flushes, ecchymosis, purpura, cerebral hemorrhage, vasculitis, vein discolouration, vein distended, wound hemorrhage, pulmonary hypertension, cerebrovascular accident.
Respiratory, thoracic and mediastinal disorders	
Very Common:	dyspnoea.
Common:	epistaxis, dyspnoea exertional, cough, rhinorrhoea.
Uncommon:	nasal congestion, wheezing, pleural effusion, hoarseness, chest wall pain, hypoxia, pulmonary congestion, rhinitis, asthma, hyperventilation, orthopnoea, sinus pain, throat tightness, productive cough, respiratory alkalosis, respiratory arrest, tachypnoea.
*Gastrointestinal disorders (see **section 4.4 Special warnings and precautions for use**)*	
Very Common:	nausea, diarrhoea, vomiting, constipation
Common:	abdominal pain, dyspepsia, loose stools, abdominal pain upper, flatulence, abdominal distension, hiccups, mouth ulceration, pharyngolaryngeal pain, stomatitis, dry mouth.
Uncommon:	ileus paralytic, abdominal discomfort, eructation, gastrointestinal motility disorder, oral pain, retching, antibiotic associated colitis, change in bowel habit, diarrhoea haemorrhagic, gastrointestinal haemorrhage, spleen pain, colitis, dysphagia, oesophagitis, gastritis, gastro-oesophageal reflux disease, gastrointestinal pain, gingival bleeding, gingival pain, haematemesis, hiatus hernia, irritable bowel syndrome, oral mucosal petechiae, rectal haemorrhage, salivary hypersecretion, tongue coated, tongue discolouration, enteritis, faecal impaction, acute pancreatitis.
*Hepatobiliary disorders (see **section 4.4 Special warnings and precautions for use**)*	
Uncommon:	hyperbilirubinaemia, hepatitis, hepatic haemorrhage, hypoproteinaemia

Skin and subcutaneous tissue disorders	
Very Common:	rash.
Common:	pruritus, erythema, periorbital oedema, urticaria, rash pruritic, sweating increased, dry skin, eczema.
Uncommon:	night sweats, rash erythematous, alopecia, contusion, pruritus generalised, rash macular, rash papular, skin nodule, rash generalized, dermatitis, eyelid oedema, nail disorder, photosensitivity reaction, skin discolouration, dermatitis atopic, hair texture abnormal, heat rash, psoriasis, vasculitic rash, face oedema, pressure sore, ichthyosis.
Musculoskeletal and connective tissue disorders	
Very Common:	myalgia.
Common:	pain in limb, muscle cramps, arthralgia, bone pain, peripheral swelling, muscle weakness, back pain, musculoskeletal pain.
Uncommon:	joint stiffness, buttock pain, joint swelling, muscle spasms, muscle twitching or sensation of heaviness, muscle stiffness, swelling, pain in jaw.
Renal and urinary disorders	
Common:	renal impairment, dysuria
Uncommon:	renal failure acute, renal colic, haematuria, proteinuria, urinary frequency, difficulty in micturition, renal failure, oliguria, urinary retention, loin pain, urinary incontinence, micturition urgency.
General disorders and administration site conditions	
Very Common:	fatigue (see **section 4.4 Special warnings and precautions for use**), pyrexia.
Common:	weakness, rigors, malaise, influenza like illness, oedema peripheral, pain, lethargy, oedema, chest pain, asthenia.
Uncommon:	fall, mucosal inflammation, feeling cold, chest pressure sensation, injection site phlebitis, mucosal haemorrhage, tenderness, injection site erythema, neuralgia, chest discomfort, groin pain, chest tightness, extravasation inflammation.
Investigations	
Common:	weight decreased, blood lactate dehydrogenase increased.
Uncommon:	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, blood urea increased, gamma-glutamyltransferase increased, blood amylase increased, blood bilirubin increased, blood phosphate decreased, liver function tests abnormal, red blood cell count decreased, weight increased, white blood cell count decreased, blood bicarbonate decreased, heart rate irregular, C-reactive protein increased.

Injury, poisoning and procedural complications	
Uncommon:	catheter related complications, post procedural pain, post procedural haemorrhage, burns.
Reproductive system and breast disorders	
Uncommon:	testicular pain, erectile dysfunction
Potentially immunocomplex-mediated reactions (see ***4.4 Special warnings and precautions for use***)	
Uncommon:	potentially immunocomplex-mediated reactions, such as serum-sickness – type reaction, polyarthritis with rash and proliferative glomerulonephritis.

Summary of Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma

Table 15 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received BORTEZOMIB (1.3 mg/m^2) administered IV in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (BR-CAP) in a prospective randomized study (LYM-3002).

The incidences of Grade ≥ 3 bleeding events were similar between the 2 arms (4 patients in the BR-CAP arm and 3 patients in the R-CHOP arm). All of the Grade ≥ 3 bleeding events resolved without sequelae in the BR-CAP arm.

Infections were reported for 31% of patients in the BR-CAP arm and 23% of the patients in the R-CHOP arm. Respiratory tract and lung infections were reported, with the predominant preferred term of pneumonia (BR-CAP 8% versus R-CHOP 5%).

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-BORTEZOMIB treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n=1) of patients receiving BORTEZOMIB in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP). The overall incidence of hepatitis B infections was similar in patients treated with BR-CAP or with R-CHOP (0.8% vs 1.2% respectively) (see **section 4.4 Special warnings and precautions for use**).

In general, the safety profile of BORTEZOMIB in mantle cell lymphoma was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (BR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to BORTEZOMIB alone. Notable differences in the mantle cell lymphoma patient population as compared to patients in the multiple myeloma studies were a ≥5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Table 15: Most Commonly Reported Adverse Reactions (≥ 5%) with Grades 3 and ≥ 4 Intensity in the Mantle Cell Lymphoma Study of BR-CAP versus R-CHOP (N=482) (Study LYM-3002)

	BR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and lymphatic system disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anaemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous system disorders						
Peripheral sensory neuropathy	53 (22)	11 (5)	1 (< 1)	45 (19)	6 (3)	0
Neuropathy peripheral	18 (8)	4 (2)	0	18 (7)	2 (1)	0
Hypoaesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paraesthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (< 1)	0	0
General disorders and administration site conditions						
Fatigue	43 (18)	11 (5)	1 (< 1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (< 1)	18 (7)	1 (< 1)	0
Oedema peripheral	16 (7)	1 (< 1)	0	13 (5)	0	0
Gastrointestinal disorders						
Nausea	54 (23)	1 (< 1)	0	28 (12)	0	0
Constipation	42 (18)	1 (< 1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (< 1)
Diarrhoea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (< 1)
Vomiting	24 (10)	1 (< 1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and subcutaneous tissue disorders						
Alopecia	31 (13)	1 (< 1)	1 (< 1)	33 (14)	4 (2)	0

		BR-CAP n=240			R-CHOP n=242	
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Metabolism and nutrition disorders						
Hyperglycaemia	10 (4)	1 (< 1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (< 1)	0
Hypokalaemia	11 (5)	3 (1)	1 (< 1)	6 (2)	1 (< 1)	0
Vascular disorders						
Hypertension	15 (6)	1 (< 1)	0	3 (1)	0	0
Psychiatric disorders						
Insomnia	16 (7)	1 (< 1)	0	8 (3)	0	0
Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; BR-CAP=BORTEZOMIB rituximab, cyclophosphamide, doxorubicin, and prednisone.						

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB.

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the BR-CAP arm. The incidence of herpes zoster among patients in the BR-CAP arm was 4.6% for patients not administered antiviral prophylaxis compared to 0.8% for patients administered antiviral prophylaxis.

Antiviral prophylaxis was administered to 102 of 242 patients (42%) in the R-CHOP arm. The incidence of herpes zoster among patients in the R-CHOP arm was 2.1% for patients not administered antiviral prophylaxis compared to 0% for patients administered antiviral prophylaxis.

Post Marketing Experience

Clinically significant adverse reactions are listed if they have been reported during post approval use of BORTEZOMIB. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders

Rare: disseminated intravascular coagulation

Very rare: thrombotic microangiopathy.

Cardiac disorders

atrioventricular block complete, cardiac tamponade, pericarditis, ventricular arrhythmias, sinus and ventricular tachycardia.

Ear and labyrinth disorders

Rare: deafness bilateral.

Eyes disorder

Rare: ophthalmic herpes, optic neuropathy, blindness, chalazion/blepharitis.

Gastrointestinal disorders

Uncommon: intestinal obstruction

Rare: ischemic colitis, acute pancreatitis.

Hepatobiliary disorders

Rare: liver failure

Infections and infestations

Rare: herpes meningoencephalitis, septic shock

Very Rare: progressive multifocal leukoencephalopathy[a]

Immune system disorders

Rare: angioedema

Very rare: anaphylactic reaction

Nervous system disorders

Rare: encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome

Unknown: Guillain-Barre Syndrome[b].

Respiratory, thoracic and mediastinal disorders

Rare: acute diffuse infiltrative pulmonary disease (see **section 4.4 Special warnings and precautions for use**), pulmonary hypertension

Skin and subcutaneous tissue disorders

Rare: acute febrile neutrophilic dermatosis (Sweet's syndrome)

Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis

[a] Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with BORTEZOMIB.

[b] GBS has been reported in patients treated with bortezomib in the post-market setting with an unknown frequency, causality has not been established.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

Cardiovascular safety pharmacology studies in monkeys and dogs showed that IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive ionotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

In patients, overdosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for BORTEZOMIB overdosage. In the event of overdosage, patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or ionotropic agents) and body temperature (see **sections 4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use**).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Bortezomib is a reversible inhibitor of 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 intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis which can affect multiple signalling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro.* Bortezomib causes a delay in tumour growth *in vivo* in nonclinical 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.

Clinical trials

All response and progression data listed below for both previously untreated multiple myeloma in non-transplant eligible patients and relapsed / refractory multiple myeloma were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. The response and progression data for transplant-eligible multiple myeloma patients were assessed using the International Myeloma Working Group (IMWG) criteria.

Previously Untreated Multiple Myeloma

Transplant Eligible

The safety and efficacy of BORTEZOMIB, as induction therapy prior to stem cell transplantation in previously untreated multiple myeloma patients, has been assessed in two Phase III trials.

A Phase III, randomised (1:1), open-label, multi-centre study conducted by the Italian Myeloma Network - GIMEMA, randomised 480 transplant-eligible patients under the age of 65 to receive three 3-week cycles of BORTEZOMIB (1.3 mg/m^2, days 1, 4, 8, 11) in combination with thalidomide (100 mg, days 1-14 in cycle 1, then 200 mg daily) and dexamethasone (40 mg, days 1, 2, 4, 5, 8, 9, 11, 12) (B-TD), or thalidomide and dexamethasone (TD) prior to tandem autologous transplant. Three months following transplant, patients received two cycles of consolidation treatment; patients randomized to receive B-TD induction received two 35-day

cycles of BORTEZOMIB (1.3 mg/m^2, days 1, 8, 15, 22), thalidomide (100 mg daily) and dexamethasone (40 mg, days 1, 2, 8, 9, 15, 16, 22, 23) consolidation; patients randomized to receive thalidomide-dexamethasone induction received two 35-day cycles of thalidomide-dexamethasone consolidation. The primary endpoint of the study was response rate ≥ nCR following induction therapy.

Patients randomized to B-TD arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the thalidomide-dexamethasone arm following induction treatment. This difference was maintained following both transplant and consolidation therapy. Response rates are presented in **Table 16**.

Table 16: Summary of Response Rates by IMWG criteria in the GIMEMA study

Response Rate n (%)	B-TD n=236	TD n=238	*p*-value
Post-induction Therapy*			
CR	44 (19)	11 (5)	<0.0001
CR+nCR**	73 (31)	27 (11)	<0.0001
≥ VGPR	146 (62)	66 (28)	<0.0001
≥ PR	220 (93)	187 (79)	<0.0001
MR/SD	16 (7)	39 (16)	0.0011
PD	0	12 (5)	0.0005
Post-first ASCT			
CR	89 (38)	54 (23)	0.0004
CR+nCR	123 (52)	74 (31)	<0.0001
≥ VGPR	186 (79)	137 (58)	<0.0001
≥ PR	220 (93)	201 (84)	0.0025
MR/SD	15 (6)	20 (8)	0.3941
PD	1 (0)	17 (7)	0.0001
Post-second ASCT			
CR	98 (42)	72 (30)	0.0105
CR+nCR	130 (55)	98 (41)	0.0024
≥ VGPR	193 (82)	152 (64)	<0.0001
≥ PR	220 (93)	199 (84)	0.0011
MR/SD	14 (6)	19 (8)	0.3804
PD	2 (1)	20 (8)	0.0001
Post-consolidation			
CR	116 (49)	82 (34)	0.0012
CR+nCR	147 (62)	108 (45)	0.0002
≥ VGPR	201 (85)	162 (68)	<0.0001
≥ PR	218 (92)	201 (84)	0.0071
MR/SD	12 (5)	16 (7)	0.4495
PD	6 (3)	21 (9)	0.0032
Best overall response			
CR	136 (58)	97 (41)	0.0001
CR+nCR	168 (71)	128 (54)	<0.0001
≥ VGPR	210 (89)	175 (73.5)	<0.0001
≥ PR	227 (96)	212 (89)	0.0074

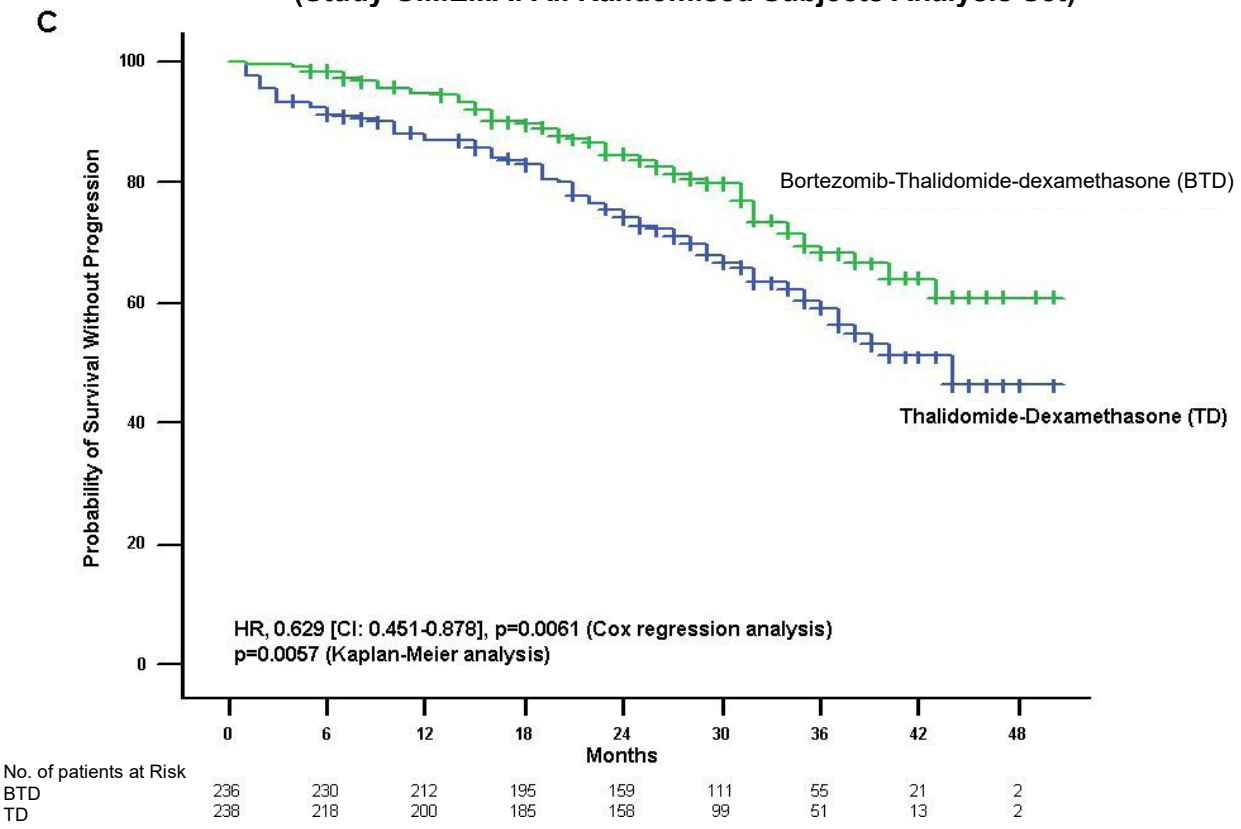
Similar differences in post-induction response rates were reported by study investigators (CR+nCR: 32% vs. 13%, p<0.0001). Differences in RR following transplantation and consolidation by investigator assessment were also similar to those centrally assessed.

** These significant differences in CR+nCR rates between arms were maintained following cyclophosphamide to collect peripheral blood stem cells (42% vs 21%, p<0.0001).

ASCT: autologous stem cell transplantation; CR: complete response; MR: minimal response; nCR: near- complete response; PD: progressive disease; PR: partial response; SD: stable disease; TD = thalidomide-dexamethasone; VGPR: very good partial response; B-TD: BORTEZOMIB -thalidomide- dexamethasone

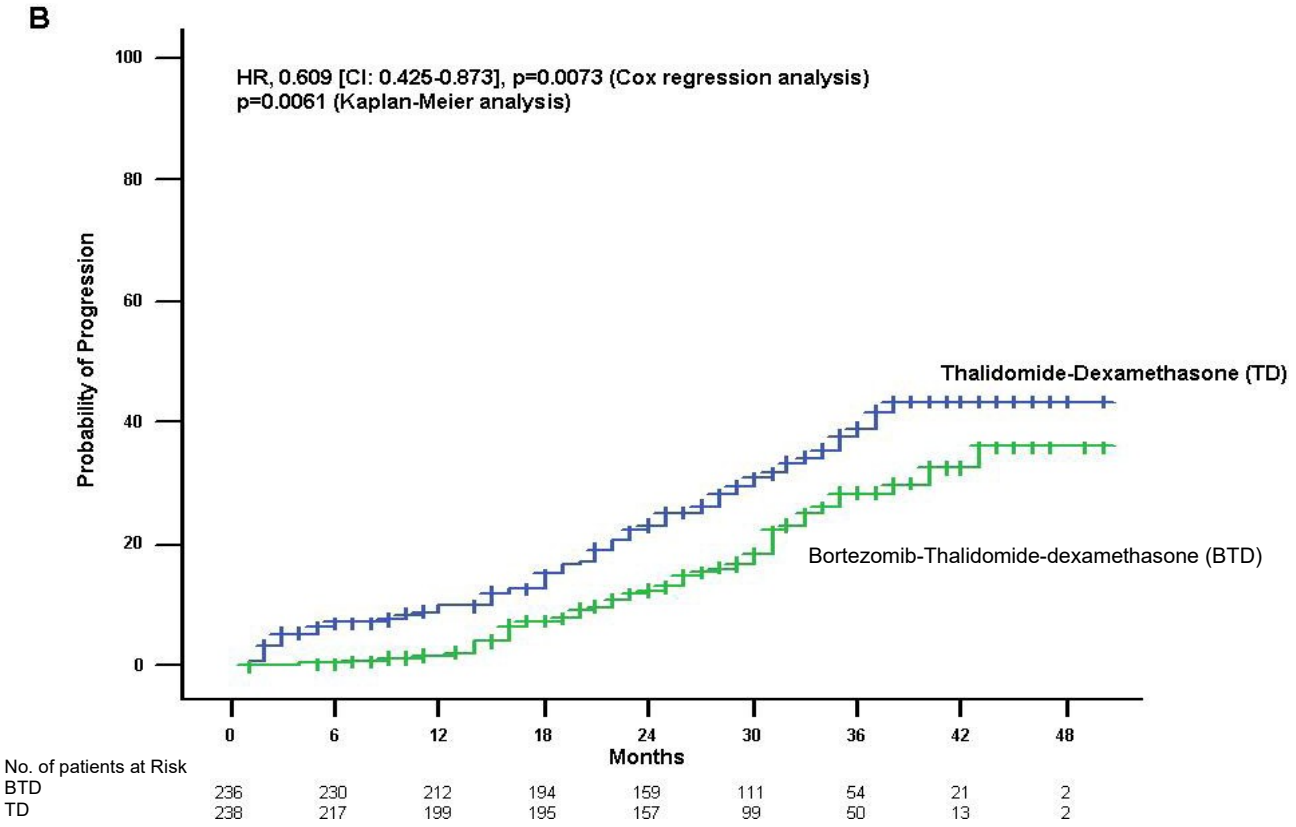
In addition, compared with the TD arm, Progression Free Survival (PFS) was also significantly longer for patients randomized to the B-TD arm (HR, 0.629 [CI: 0.451-0.878], *p*=0.0061). The estimated 3-year PFS rate was 68% in the VTD arm and 56% in TD (*p*=0.0057) (see **Figure 1**). 58 (24.5%) and 86 (36%) patients progressed or died, respectively. The estimated 3-year probability of progression or relapse was 29% in the B-TD versus 39% in the TD arm (HR, 0.609 [CI: 0.425-0.873], *p*=0.0073; *p*=0.0061 by Kaplan-Meier analysis) (see **Figure** 2).

Figure 1: Progression-Free Survival
(Study GIMEMA: All Randomised Subjects Analysis Set)



No. of patients at Risk									
BTD	236	230	212	195	159	111	55	21	2
TD	238	218	200	185	158	99	51	13	2

Figure 2: Time to Disease Progression
(Study GIMEMA: All Randomised Subjects Analysis Set)



The IFM-2005, Phase III, randomised (1:1:1:1), multi-centre, open-label study was conducted to compare the efficacy and safety of BORTEZOMIB-dexamethasone (B-Dex) and vincristine-doxorubicin-dexamethasone (VAD) as induction therapy prior to HDT-ASCT, and to evaluate the impact of post-induction consolidation therapy. Patients in this study were randomised to receive VAD plus no consolidation (arm A1), VAD plus dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP) consolidation (arm A2), B-Dex plus no consolidation (arm B1), or B-Dex plus DCEP consolidation (arm B2).

A total of 482 patients aged ≤65 years were randomised; 240 patients received four 3-week cycles of BORTEZOMIB (1.3 mg/m^2), days 1, 4, 8 and 11 plus dexamethasone (40 mg) days 1-4 (all cycles) and days 9-12 (cycles 1 and 2), while 242 patients received four 4-week cycles of VAD. The primary endpoint of this study was the CR/nCR rate post-induction.

Patients randomized to the B-Dex arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the VAD arm following induction treatment. Based on an intention to treat analysis, response rates were similar regardless of whether patients received DCEP consolidation or not. Efficacy results are presented in **Table 17**:

Table 17: Response to induction therapy (overall) in the IFM2005 study*			
	VAD (A1+A2) N=242	**B-Dex (B1+B2) N=240**	***p*-value**
Evaluable population, N	**218**	**223**	
ORR (≥PR), n (%)	137 (62.8)	175 (78.5)	<0.001
	VAD (A1+A2) N=242	**B-Dex (B1+B2) N=240**	***p*-value**
≥VGPR	33 (15.1)	84 (37.7)	<0.001
CR/nCR	14 (6.4)	33 (14.8)	0.004
CR	3 (1.4)	13 (5.8)	0.012
MR+SD	58 (26.6)	28 (12.6)	
PD	9 (4.1)	10 (4.5)	
Death	6 (2.8)	1 (0.5)	
Not assessable	8 (3.7)	9 (4.0)	

A total of 184/218 (84.4%) and 197/223 (88.3%) evaluable patients who received VAD and B-Dex induction, respectively, underwent autologus stem cell transplantation. The number of patients who received a second transplantation was 41 (20.8%) in the B-Dex arm, compared to 50 (27.2%) for patients in the VAD arm. Post-transplant response rates are shown in **Table 18**.

Table 18: Response rates post-transplantation*			
	VAD (A1+A2) N=218	**B-Dex (B1+B2) N=223**	***p*-value**
Response to first transplant			
ORR (≥PR), n (%)	168 (77.1)	179 (80.3)	0.401
≥VGPR	81 (37.2)	121 (54.3)	<0.001
CR/nCR	40 (18.4)	78 (35.0)	<0.001
CR	19 (8.7)	36 (16.1)	0.016
MR+SD+PD	8 (3.7)	6 (2.7)	
Death	2 (0.9)	1 (0.5)	
No transplantation	34 (15.6)	26 (11.7)	
Overall, including second transplantation			
≥VGPR	102 (46.7)	151 (67.7)	<0.001
CR/nCR	49 (22.5)	88 (39.5)	<0.001

* All response assessments were confirmed by an Independent Review Committee.
CR: complete response; MR: minimal response; nCR: near-complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response.

In addition, the median PFS was 29.7 months among patients who received VAD versus 36.0 months among patients who received B-Dex induction, with 128 (52.9%) of 242 and 110 (45.8%) of 240 patients, respectively, having progressed ($p = 0.064$, or $p = 0.057$ if adjusted for initial stratification factors) after median follow-up of 31.2 months.

Non-Transplant Eligible

The VISTA study is a prospective phase III, international, randomized (1:1), open-label clinical study of 682 patients, conducted to determine whether BORTEZOMIB (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma unsuitable for high dose chemotherapy with stem cell transplantation. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in **Table 19**.

Table 19: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**BMP N=344**	**MP N=338**
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51% / 49%	49% / 51%
Race: Caucasian/asian/black/other	88% / 10% / 1% / 1%	87% / 11% / 2% / 0%
Karnofsky performance status score ≤70	35%	33%
Hemoglobin <100 g/L	37%	36%
Platelet count <75 x 10^9/L	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%
Median β_2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤30 mL/min [n (%)]	20 (6%)	16 (5%)
BMP = BORTEZOMIB + melphalan + prednisone; MP = melphalan + prednisone		

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered BMP treatment. Survival continued to be followed after the interim analysis. Median follow-up in the initial analysis (**Table 20** and **Figure 1**) was 16.3 months. Median follow-up in the last survival analysis (**Figure 2**) was 36.7 months. Median overall survival in the MP arm was 43.1 months and was not reached in the BMP arm. Fifty percent of subjects in the MP arm subsequently received BORTEZOMIB.

Table 20: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**BMP n=344**	**MP n=338**
Time to Progression – Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value [c]	0.000002	
Progression-free Survival Events n (%)	135 (39)	190 (56)

Efficacy Endpoint	BMP n=344	MP n=338
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall Survival Events (deaths) n (%)	45 (13)	76 (23)
Hazard ratio[b] (95% CI)	0.61 (0.42, 0.88)	
p-value [c]	0.00782	
Response Rate population[e] n = 668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in Serum M-protein population[g] n=667	n=336	n=331
>=90% n (%)	151 (45)	34 (10)
Time to First Response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] Response Duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to Next Therapy Events n (%)	73 (21)	127 (38)
Median[a] (95% CI)	NE (26.1, NE)	20.8 mo (18.3, 28.5)
Hazard ratio[b] (95% CI)	0.52 (0.39, 0.70)	
p-value [c]	0.000009	

[a] Kaplan-Meier estimate.

[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for BMP

[c] *p*-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region

[d] *p*-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

[e] Response population includes patients who had measurable disease at baseline

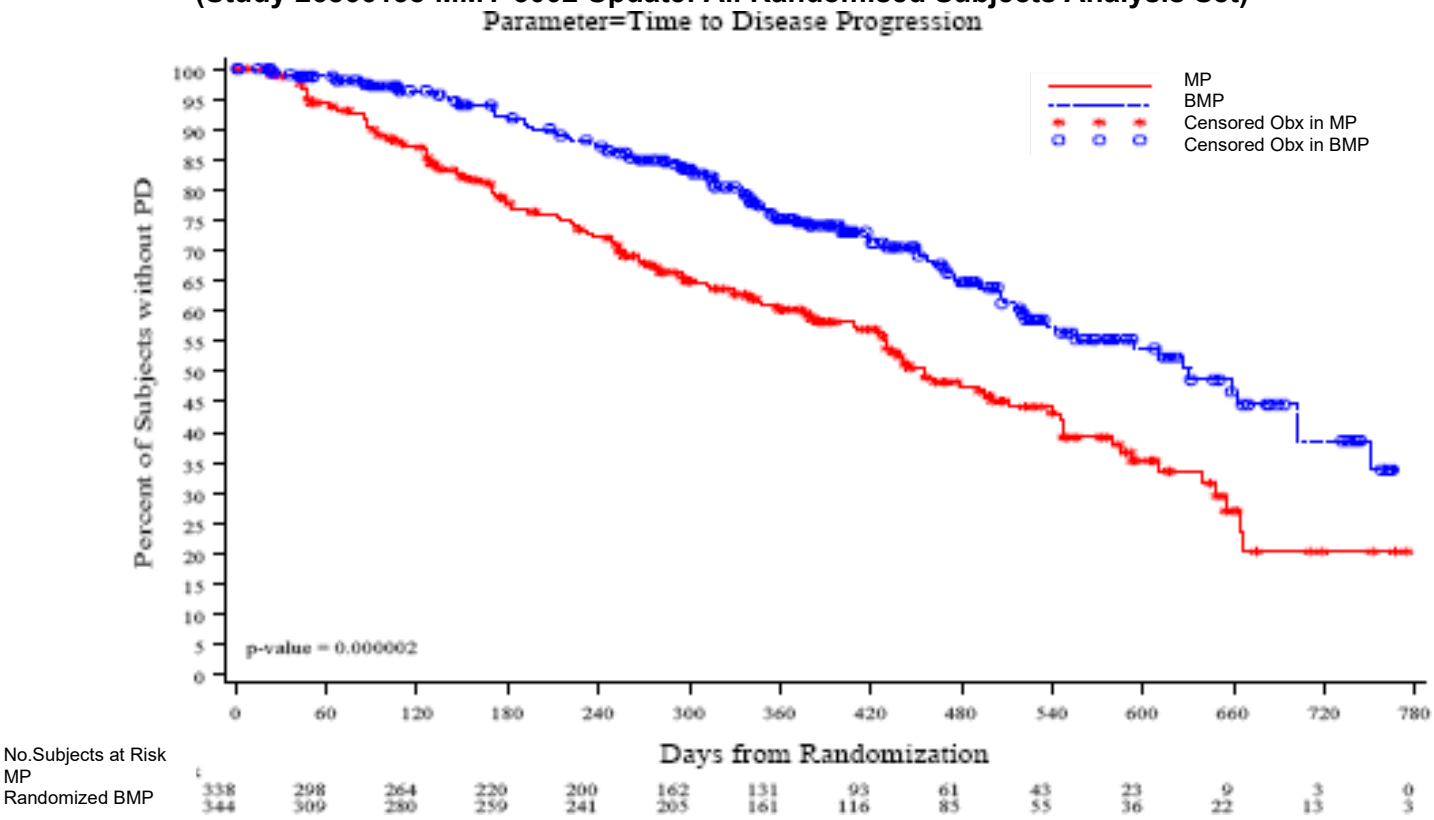
[f] EBMT criteria

[g] All randomized patients with secretory disease

NE: Not estimable

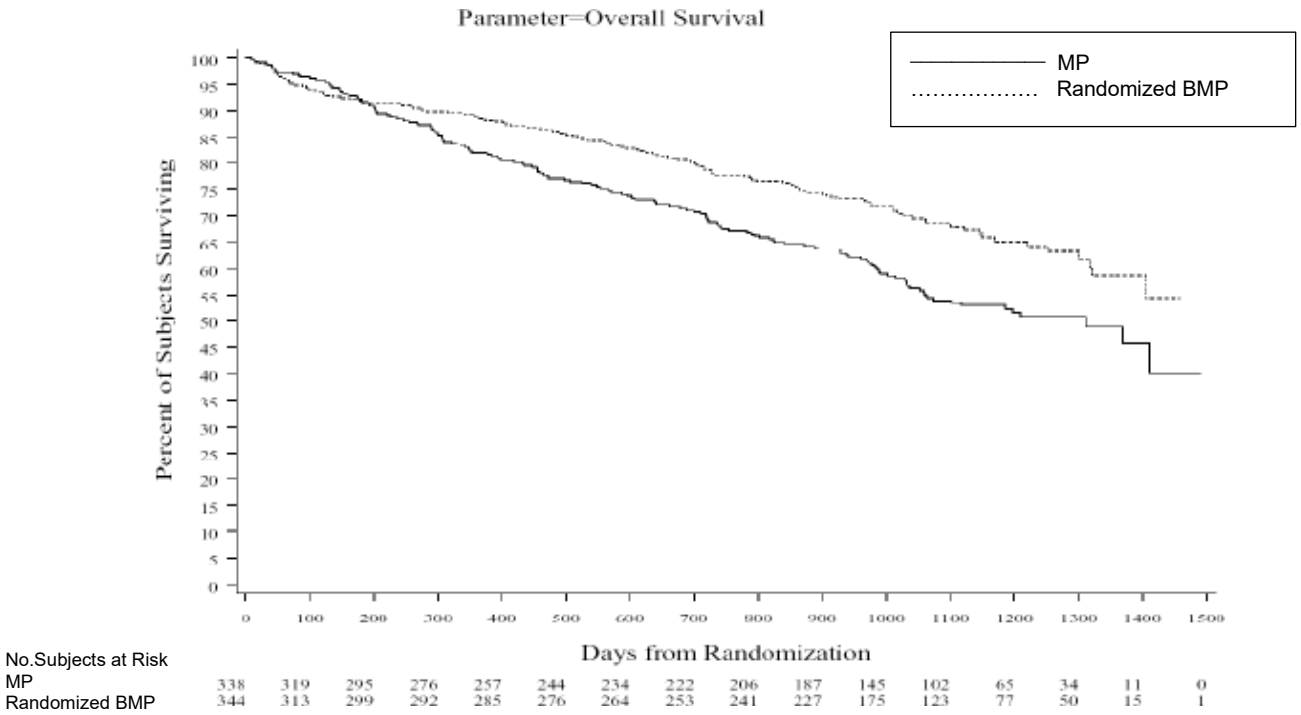
The time to progression (TTP) was significantly longer on the BORTEZOMIB arm (see **Figure 3**)

Figure 3: Time to Disease Progression
(Study 26866138-MMY-3002 Update: All Randomised Subjects Analysis Set)



A significant survival advantage is shown with BORTEZOMIB (see **Figure 4**)

Figure 4: Overall Survival
(Study 26866138-MMY-3002 Update: All Randomised Subjects Analysis Set)



Relapsed / Refractory Multiple Myeloma

The safety and efficacy of BORTEZOMIB were evaluated in 2 studies at the recommended dose of 1.3 mg/m^2: The APEX study - a phase III randomised, stratified, open-label, comparative study, versus Dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a phase II single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment (see **Table 21** and **Table 22**).

Table 21: Dosing regimens in the APEX and Phase II studies

Phase/arm	Drug Schedule	Dose	Regimen
II	BORTEZOMIB: Day 1,4,8,11 (rest Day 12-21)	1.3 mg/m^2 (IV bolus)	Q3 weeks x 8 cycles (extension**)
III (APEX)	BORTEZOMIB* a) Days 1,4,8,11 (Rest Day 12-21) b) Days 1,8,15,22 (Rest Day 23-35)	1.3 mg/m^2 (IV bolus)	a) Q3 weeks x 8, then b) Q5 weeks x 3
III (APEX)	DEXAMETHASONE a) Days 1–4, 9–12, 17–20 Days 1–4	40 mg (PO)	a) Q5 weeks x 4 b) Q4 weeks x 5
II	Add DEXAMETHASONE***	20 mg (PO) (Days 1,2,4,5,8,9,11,12)	Q3 weeks

* a) is the initial treatment, a) and b) represent a full course of treatment

** An extension study authorised patients benefiting from treatment to continue receiving BORTEZOMIB

*** If after 2 or 4 cycles of BORTEZOMIB, the patients had progressive disease or stable disease, respectively, they could receive dexamethasone

Table 22: Patient characteristics in the Phase II* and APEX Studies

	Phase II study BORTEZOMIB N=202	APEX study BORTEZOMIB N=333	APEX study DEX. N=336
Patient characteristics			
Median age in years (range)	59(34-84)	62.0 (33-84)	61.0 (27-86)
Gender: male/female	60% / 40%	56% / 44%	60% / 40%
Karnofsky Performance Status score ≤ 70	20%	13%	17%
Haemoglobin <100 g/L	44%	32%	28%
Platelet count <75 x 10^9/L	21%	6%	4%
Disease Characteristics			
Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%	60%/23%/12%	59%/24%/13%
Median β2-microglobulin (mg/L)	3.5	3.7	3.6
Median creatinine clearance (mL/min)	73.9	73.3	75.3
Abnormal cytogenetics	35%		

	Phase II study BORTEZOMIB N=202	APEX study BORTEZOMIB N=333	APEX study DEX. N=336
Chromosome 13 abnormalities	15%	25.7%	25.0%
Median Duration of Multiple Myeloma Since Diagnosis in Years	**4.0**	**3.5**	**3.1**
Previous Therapy			
Number of Prior Therapeutic Lines of Treatment			
Median (range)**	6 (2-15)	2 (1-7)	2 (1-8)
1 prior line	0	40%	35%
>1 prior line		60%	65%
All patients			
Any prior steroids, e.g., dexamethasone, VAD	99%	98%	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%	91%	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%	77%	76%
Any prior thalidomide therapy	83%	48%	50%
Any prior stem cell transplant/other high-dose therapy	64%	67%	68%
Prior experimental or other types of therapy	44%	3%	2%

*Based on number of patients with baseline data available

**Including steroids, alkylating agents, anthracyclines, thalidomide and stem cell transplants

APEX Study (Phase III)

In the APEX study described above, patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline grade ≥ 2 peripheral neuropathy or platelet counts <50,000/µL. A total of 627 patients were evaluable for response. Stratification factors were based on the number of lines of prior therapy the patient had previously received (1 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during or within 6 months of stopping their most recent therapy versus relapse >6 months after receiving their most recent therapy), and screening β_2-microglobulin levels (≤ 2.5 mg/L versus >2.5 mg/L).

Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered BORTEZOMIB, regardless of disease status. At this time of study termination, a final statistical analysis was performed. Due to this early termination of the study, the median duration of follow-up for surviving patients (n=534) is limited to 8.3 months. The time to event analyses and response rates from the APEX trial are presented in **Table 23**.

Table 23: Summary of Efficacy Analyses in the APEX Study						
	All Patients		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**	
	BORTEZOMIB	**Dex**	**BORTEZOMIB**	**Dex**	**BORTEZOMIB**	**Dex**
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=200**	**n=217**
Time to Progression – Events n (%)	147(44)	196(58)	55(42)	64(54)	92(46)	132(61)
Median[a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (2.8, 3.5)
Hazard ratio[b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value[c]	<0.0001		0.0019		<0.0001	
Overall survival Events (deaths) n (%)	51(15)	84(25)	12(9)	24(20)	39(20)	60(28)
Hazard ratio[b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value[c, d]	<0.05		<0.05		<0.05	
Response Rate population[e] n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR[f] n(%)	20(6)	2(<1)	8(6)	2(2)	12(6)	0(0)
PR[f] n(%)	101(32)	54(17)	49(38)	27(25)	52(28)	27(13)
nCR[f,g] n(%)	21(7)	3(<1)	8(6)	2(2)	13(7)	1(<1)
CR + PR[f] n(%)	121(38)	56(18)	57(45)	29(26)	64(34)	27(13)
p-value[h]	<0.0001		0.0035		<0.0001	
Median Response Duration						
CR[f]	9.9 mo	NE[i]	9.9 mo	NE	6.3 mo	NA[j]
nCR[f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR[f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[a] Kaplan-Meier estimate

[b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for BORTEZOMIB

[c] *p*-value based on the stratified log-rank test including randomisation stratification factors.

[d] Precise *p*-value cannot be rendered

[e] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study dose

[f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria, nCR in the PR category.

[g] In 2 patients, the IF was unknown.

[h] *p*-value for Response Rate (CR + PR) from the Cochrane-Mantel-Haenszel chi-square test adjusted for the stratification factors;

[i] Not Estimable.

[j] Not Applicable, no patients in category.

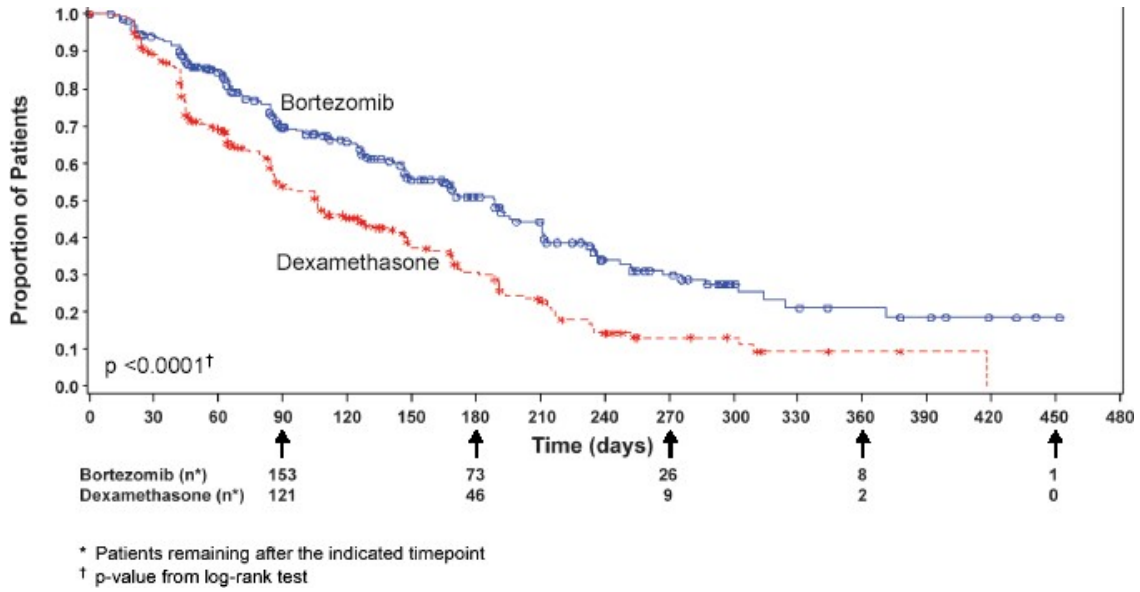
For the 121 patients achieving a response (CR or PR) on the BORTEZOMIB arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm.

Treatment with BORTEZOMIB led to a significantly longer TTP, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone in patients who have received more than one prior therapy as well as in patients who have received only one prior line of therapy.

Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the BORTEZOMIB arm. Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for BORTEZOMIB independently of age. Regardless of β2- microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the BORTEZOMIB arm.

The time to progression (TTP) was significantly longer on the BORTEZOMIB arm (see **Figure 5**).

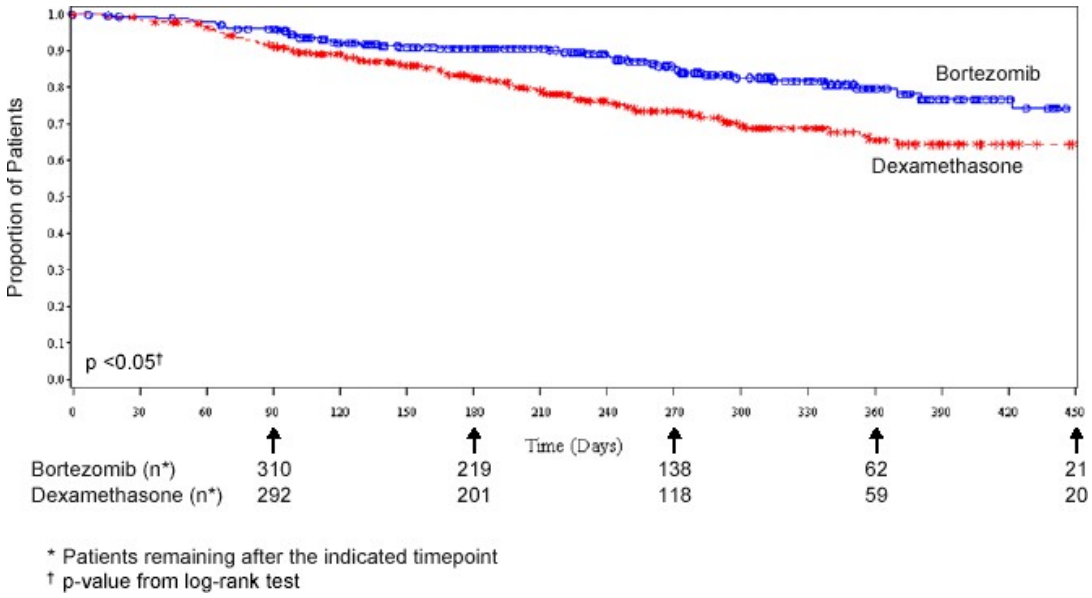
Figure 5: Time to progression
Bortezomib vs Dexamethasone



As shown in **Figure 6**, BORTEZOMIB had a significant survival advantage relative to dexamethasone (p<0.05). The median follow-up was 8.3 months.

Figure 6: Overall Survival

Bortezomib vs Dexamethasone



* Patients remaining after the indicated timepoint
† p-value from log-rank test

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing BORTEZOMIB IV and SC

An open label, randomized, phase III non-inferiority study compared the efficacy and safety of the subcutaneous administration (SC) of BORTEZOMIB versus the intravenous administration (IV). This study included 222 patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of BORTEZOMIB by either the SC or IV route for 8 cycles. Patients who did not obtain an optimal response (less than Complete Response CR) to therapy with BORTEZOMIB alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and day after BORTEZOMIB administration. Patients with baseline grade ≥ 2 peripheral neuropathy or platelet counts <50,000/µL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (1 previous line versus more than 1 line of therapy), and international staging system (ISS) stage (incorporating beta$_2$-microglobulin and albumin levels; Stages I, II, or III). The baseline patient and disease characteristics were comparable between the SC and IV arms.

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent BORTEZOMIB for both the SC and IV routes, with an ORR of 42% in both groups. In addition, all secondary endpoints relating to efficacy showed comparable results between SC and IV administration (**Table 24**).

Table 24: Summary of efficacy analyses for the SC administration of BORTEZOMIB compared to IV

	IV BORTEZOMIB	**SC BORTEZOMIB**
Response Evaluable Population	**n=73**	**n=145**
Response Rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value [(a)]	0.00201	
CR n (%)	6(8)	9(6)
PR n (%)	25(34)	52(36)
nCR n (%)	4(5)	9(6)

	IV BORTEZOMIB	SC BORTEZOMIB
Response Rate at 8 cycles		
ORR (CR+PR)	38(52)	76(52)
p-value [(a)]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29(40)	61(42)
nCR n (%)	7(10)	14(10)
Intent to Treat Population [(b)]	n=74	n=148
TTP, months	9.4	10.4
(95% CI)	(7.6,10.6)	(8.5,11.7)
Hazard ratio (95% CI) [(c)]	0.839 (0.564,1.249)	
p-value [(d)]	0.38657	
Progression Free Survival, months	8.0	10.2
(95% CI)	(6.7,9.8)	(8.1,10.8)
Hazard ratio (95% CI) [(c)]	0.824 (0.574,1.183)	
p-value [(d)]	0.295	
1-year Overall Survival (%)[(e)]	76.7	72.6
(95% CI)	(64.1,85.4)	(63.1,80.0)

(a) *p*-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.
(b) 222 subjects were enrolled into the study; 221 subjects were treated with BORTEZOMIB
(c) Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.
(d) Log rank test adjusted for stratification factors: ISS staging and number of prior lines.
(e) Median duration of follow up is 11.8 months

Table 25 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after cycle 4.

Dexamethasone had a similar effect on improvement of response on both treatment arms:

- 30% (SC) and 30% (IV) of patients with no response at end of Cycle 4 obtained a response later in subsequent cycles (cycle 5 through 8).
- 13% (SC) and 13% (IV) of patients with PR at end of Cycle 4 obtained a CR later in subsequent cycles (cycle 5 through 8).

Table 25: Cross-tabulation of Summary of Best Response After 4 Cycles vs. After 8 Cycles for patients who received dexamethasone

		---------- Best Response After 8 Cycles ---------- (N=121)		
Treatment Group	**Total**	---------- Category, n (%) ----------		
Cycle 4 Best Response *	n (%)	CR	PR	Non-responders
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)	0	0
PR	31 (26)	4 (13)	27 (87)	0
Non-responder	47 (39)	0	14(30)	33 (70)

*Response assessment by validated computer algorithm. This algorithm incorporates a consistent assessment of all data required for response by the modified EBMT criteria.

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from cycle 5 onwards, were higher than observed in prior registration study with single agent IV BORTEZOMIB, APEX, (38% ORR and median TTP of 6.2 months for the BORTEZOMIB arm). Time to Progression and ORR was also higher compared to the subgroup of patients on APEX that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (**Table 20**).

Phase II studies

The safety and efficacy of bortezomib were evaluated in an open-label, single-arm, multi-centre study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Dosing regimens and baseline patient and disease characteristics are summarised in **Table 21** and **Table 22**. The study employed dose modifications for toxicity (see **section 4.2 Dose and method of administration**). Responses to BORTEZOMIB alone in the phase II study are shown in **Table 26**.

In general, patients who had confirmed Complete Response received 2 additional cycles of BORTEZOMIB treatment beyond confirmation. The median time to response was 38 days (range 30 to 127 days). The median survival of all patients enrolled was 16 months (range <1 to 18+ months). The response rate to BORTEZOMIB was independent of the number and types of prior therapies.

Table 26: Summary of disease outcomes in Phase II study

Response Analyses (BORTEZOMIB monotherapy) N=188	**N (%)**	**(95% CI)**
Overall Response Rate (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[1]	5 (2.7%)	(1,6)
Partial Response (PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[1]**Complete Response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

[2]**Partial Response** required ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

[3]**Clinical remission (SWOG)** required ≥ 75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

Patients who did not obtain an optimal response to therapy with BORTEZOMIB alone were able to receive high-dose dexamethasone in conjunction with BORTEZOMIB (i.e., 40 mg dexamethasone with each dose of BORTEZOMIB administered orally as 20 mg on the day of and 20 mg the day after BORTEZOMIB administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160 mg over 3 weeks. Eighteen percent (13/74) of patients achieved or had an improved

response (CR 11% or PR 7%) with combination treatment.

A small dose-response study was performed in 54 patients with multiple myeloma who received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

Previously Untreated Mantle Cell Lymphoma

Study LYM-3002 was a Phase III, randomized, open-label study comparing the efficacy and safety of the combination of BORTEZOMIB, rituximab, cyclophosphamide, doxorubicin, and prednisone (BR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=244) in adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV). Patients of median age 66 years enrolled in this trial were either ineligible (e.g. due to age or comorbidity; n = 407) or were not considered (e.g. due to transplant unavailability, financial unaffordability or patient refusal, despite being medically eligible; n = 80) for stem-cell transplantation.
Patients in the BR-CAP treatment arm received BORTEZOMIB (1.3 mg/m^2 IV) on Days 1, 4, 8, 11 (rest period days 12-21), rituximab (375 mg/m^{2}IV) on Day 1; cyclophosphamide (750 mg/m^2 IV) on Day 1; doxorubicin (50 mg/m^2 IV) on Day 1; and prednisone (100 mg/m^2 orally) on Day 1 through Day 5 of the 21 day BORTEZOMIB treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given.

The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC).

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 74% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow-up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with14% of subjects in the BR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups received 6 or more cycles of treatment, 83% in the R-CHOP group and 84% in the BR-CAP group.

A statistically significant benefit in favour of the BR-CAP treatment group was observed for the median values for PFS, TTP, TNT, TFI and overall survival, over the entire duration of the study.

At a median follow up of 40 months, a 59 % improvement in the primary endpoint of PFS [hazard ratio (HR) 0.63, 95 % CI 0.50–0.79; p < 0.001] was observed in the BR-CAP group (median = 24.7 months as compared to the R-CHOP group (median 14.4 months). The median duration of complete response was more than double in the BR-CAP group (42.1 months) compared with the R-CHOP group (18 months) and the duration of overall response was 21.4 months longer in the BR-CAP group.

At a median follow-up of 40 months, median OS (56.3 months in the R-CHOP group, and not reached in the BR CAP group) favoured the BR-CAP group, (estimated HR=0.80; p=0.173). There was a trend towards prolonged overall survival favouring the BR-CAP group; at this point in time, with the estimated 4-year survival rate was 53.9% in the R-CHOP group and 64.4% in the

BR-CAP group.

Overall survival demonstrated statistical significance in the final analysis, after a median follow-up of 82 months. Median OS in the BR-CAP group was 90.7 months, almost three years more than the OS achieved in the R-CHOP group, which was 55.7 months (HR-0.66; p=0.001).

Efficacy results are presented in **Table 27**.

Table 27: Summary of Efficacy Outcomes in a Phase 3 Mantle Cell Lymphoma Study in Previously Untreated Patients (LYM-3002)

Efficacy endpoint	**BR-CAP n=243 (ITT patients)**	**R-CHOP n=244 (ITT patients)**	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7%)	165 (67.6%)	HR[d] (95% CI)=0.63 (0.50;0.79) *p*-value[e] < 0.001
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Progression free survival (Investigator)[b]			
Events n (%)	128 (52.7%)	179 (73.4%)	HR[d] (95% CI)=0.51 (0.41; 0.65) *p*-value[e] < 0.001
Median[c] (95% CI) (months)	30.7 (25.1; 37.3)	16.1 (14.0; 18.4)	
Time to Progression[a]			
Events n (%)	114 (46.9%)	148 (60.7%)	HR[d] (95% CI)=0.58 (0.45;0.74) *p*-value[e] < 0.001
Median[c] (95% CI) (months)	30.5 (22.9; 40.9)	16.1 (13.7;18.1)	
Time to Next Anti-lymphoma Therapy			
Events n (%)	94 (38.7%)	145 (59.4%)	HR[d] (95% CI)=0.50 (0.38;0.65) *p*-value[e] < 0.001
Median[c] (95% CI) (months)	44.5 (38.8; NE)	24.8 (22.1; 27.5)	
Treatment Free Interval			
n: All Treated Patients	240	242	
Events n (%)	93 (38.8%)	145 (59.9%)	
Median[c] (95% CI) (months)	40.6 (33.6; NE)	20.5 (17.8; 22.8)	HR[d] (95% CI)=0.50 (0.38; 0.65) *p*-value[e] < 0.001
Overall survival at a median follow up of 82 months			
n: ITT patients	243	244	
Events n (%)	103 (42.4)	138 (56.6)	HRd (95% CI)=0.66 (0.51; 0.85) p-value[e] =0.001
Median[c] (95% CI) (months)	90.7 (71.4; NE)	55.7 (47.2;68.9)	
Response Rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[h] n(%)	122 (53.3%)	95 (41.7%)	OR[f] (95% CI) = 1.688 (1.148; 2.481) *p*-value[g] =0.007

Overall radiological response (CR+CRu+PR)[i] n(%)	211 (92.1%)	204 (89.5%)	OR[f] (95% CI) = 1.428 (0.749; 2.722) *p*-value[g] = 0.275
Response Duration			
Duration of complete response (CR+CRu)[j]			
n = response-evaluable patients	122	95	
Median[c] (95% CI) (months)	42.1 (30.7; 49.1)	18.0 (14.0; 23.4)	
Duration of Response (CR+CRu+PR)[k]			
n: response-evaluable subjects	211	204	
Median[c] (95% CI) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

Note: All results are based on the analysis performed at a median follow up duration of 40 months except for the overall survival analysis

[a] Based on IRC assessment (radiological data only).

[b] Based on Investigator assessment.

[c] Based on Kaplan-Meier product limit estimates.

[d] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for BR-CAP.

[e] Based on Log rank test stratified with IPI risk and stage of disease.

[f] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for BR-CAP.

[g] *P*-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.

[h] Include all CR + CRu, by IRC, bone marrow and LDH.

[i] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.

[j] Calculated from first date of complete response (CR+CRu by IRC, bone marrow and LDH) to date of PD or death due to PD.

[k] Calculated from first date of response (include all radiological CR+CRu+PR by IRC) to date of PD or death due to PD.

IRC=Independent Review Committee; IPI=International Prognostic Index; LDH = Lactate dehydrogenase; CR=Complete Response; CRu= Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio; OR= odds ratio; ITT= intent to treat; PD=Progressive disease

5.2. PHARMACOKINETIC PROPERTIES

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 first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0mg/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. 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 of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

In the PK/PD substudy in Phase III trial, following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m^2 dose to multiple myeloma patients (n = 14 for IV, n = 17 for SC), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent (151 ng.h/mL vs 155 ng.h/mL)for SC and IV administration. The C_{max} after SC administration (20.4 ng/mL) was lower than IV (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

Distribution

The mean distribution volume of bortezomib ranged from 1659 litres to 3294 litres (489 to 1884 L/m^2) following single- or repeat-dose IV 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.

Protein binding

Over a bortezomib concentration range of 10 to 1000 ng/mL, the *in vitro* protein binding averaged 83% in human plasma. The percent of bortezomib bound to plasma proteins was not concentration dependent.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, 2D6, 2C9, and 1A2. The major metabolic pathway is deboronation, with the two main metabolites formed undergoing subsequent hydroxylation. One of the two main deboronated metabolites was shown to be inactive as a 26S proteasome inhibitor. Pooled plasma data from 8 patients at 10 min and 30 min after IV dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Excretion

The elimination pathways of bortezomib have not been evaluated *in vivo*.

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. Clearance of bortezomib was comparable among all the groups. However, the number of patients with severe renal impairment was insufficient to allow reliable conclusions regarding this group (see **section 4.4 Special warnings and precautions for use**).

Hepatic Impairment

Formal studies in patients with severely impaired hepatic function have not been conducted to date; consequently caution is recommended when administering bortezomib to these classes of patients (see **section 4.4 Special warnings and precautions for use**).

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Bortezomib showed clastogenic activity at a high concentration (3 μg/mL) in an *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Clastogenic activity was not observed *in vivo* in a mouse micronucleus test using intravenous doses of up to 3 mg/m^2. Bortezomib was not genotoxic in *in vitro* tests for bacterial gene mutation.

Carcinogenicity

Carcinogenicity studies have not been conducted with bortezomib.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Mannitol.
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

Water for injections

6.2. INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in **section 4.2 Dose and method of administration**.

6.3. SHELF LIFE

Unopened vial
refer to the ARTG record

storage times and conditions are the responsibility of user.

During preparation for administration and during administration itself it is not necessary to protect the medicinal product from light.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials:

Store at 2°C to 8°C. (Refrigerate, Do not freeze. Protect from light). Keep the container in the outer carton in order to protect from light.

After opening and dilution:
BORTEZOMIB EVER PHARMA contains no antimicrobial preservative. The chemical and physical in-use stability after first opening and/or dilution has been demonstrated for:

- 28 days, when stored at 2 °C – 8 °C and protected from light
- 28 days, when stored at 25 °C and protected from light
- 24 hours, when stored at 25 °C and normal indoor lighting conditions

in the original vial and/or a polypropylene syringe.
From a microbiological point of view, unless the method of opening and/or dilution precludes the risk of microbial contamination, the product should be used immediately. To reduce microbial hazard, use as soon as possible after dilution and if storage is necessary hold at 2 - 8°C for up to 8 hours

During preparation for administration and during administration itself it is not necessary to protect the medicinal product from light.

6.5. NATURE AND CONTENTS OF CONTAINER

Colourless glass vial (type I) with a rubber stopper and an aluminium cap with plastic flip-off and sheathed in a protective plastic sleeve.

Pack sizes
BORTEZOMIB EVER PHARMA bortezomib 2.5 mg/1 mL (AUST R 345128)
2.5 mg/1 mL: 1 and 5 vials

The 1 mL vial contain an overfill of up to 1.2 mL to allow for withdrawal of the full required volume

BORTEZOMIB EVER PHARMA bortezomib 3.5 mg/1.4 mL (AUST R 345130)
3.5 mg/1.4 mL: 1 and 5 vials

The 1.4 mL vial contains an overfill of up to 1.6 mL to allow for withdrawal of the full required volume

Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Pregnant personnel should not handle this medicine.

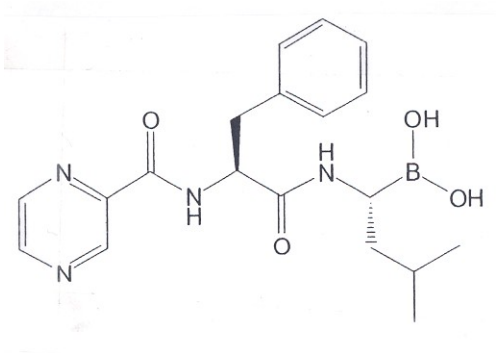
General precautions

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

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

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid

MW:384.2

Molecular Formula: $C_{19}H_{25}BN_4O_4$(monomeric boronic acid)

CAS number:

179324-69-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

13 Sep 2021

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information