Bortezomib powder for solution for injection, 3.5mg/vial

a. Brand or Product Name:
BORT SPAL 3.5
Bortezomib powder for solution for injection,3.5mg/vial

b. Strength of Active Ingredient:
Each lyophilized vial contains 3.5mg bortezomib

c. Excipients
Mannitol (Pyrogen free)
Tertiary butyl alcohol
Water for injection

d. Product description
White to off white colored lyophilized powder or cake
Description of Reconstituted solution: Clear colorless solution and free from visible particles
Diluent: Sodium chloride 9 mg/ml (0.9%) solution for injection

e. Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents,
ATC code: L01XG01
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 signaling 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 tumor growth in vivo in nonclinical tumor models, including multiple myeloma.

f. Pharmacokinetics
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1.0 mg/m^2 dose and 89 to 120 ng/ml for the 1.3 mg/m^2 dose. Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients with multiple myeloma (in intravenous and subcutaneous group), the total systemic exposure after repeat dose administration (AUClast) was equivalent for subcutaneous and intravenous administrations. The Cmax after subcutaneous administration (20.4 ng/ml) was lower than intravenous (223 ng/ml). The AUClast 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 liters to 3294 liters 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. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 - 1000 ng/mL.

Metabolism
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

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

Special Populations
Age, Gender, and Race
The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 L/hr/m^2, volume of distribution at steady-state was 834 L/m^2, and the elimination half-life was 100 hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

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

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of bortezomib during the first treatment cycle, including patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored.

Renal Impairment
In patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups:

Normal (CrCL ≥ 60 mL/min/1.73 m2, n = 12), Mild (CrCL = 40 - 59 mL/min/1.73 m2, n = 10), Moderate (CrCL = 20 - 39 mL/min/1.73 m2, n = 9), and Severe (CrCL < 20 mL/min/1.73 m2, n = 3.Patients were administered intravenous doses of 0.7 to 1.3 mg/m2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups (see Recommended Dosage).

g. Indications
BORT SPAL 3.5 is indicated for the treatment of patients with multiple myeloma.
BORT SPAL 3.5 is indicated for the treatment of patients with mantle cell lymphoma.

h. Recommended Dose
Important Dosing Guidelines
BORT SPAL 3.5 is for intravenous or subcutaneous use only. Do not administer BORT SPAL 3.5 by any other route.

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

The recommended starting dose of BORT SPAL 3.5 is 1.3 mg/m^2. BORT SPAL 3.5 may be administered intravenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5 mg/ml. BORT SPAL 3.5 retreatment may be considered for patients with multiple myeloma who had previous responded to treatment with BORT SPAL 3.5 and who have relapsed at least 6 months after completing prior BORT SPAL 3.5 treatment. Treatment may be started at the last tolerated dose. When administered intravenously, administer BORT SPAL 3.5 as a 3 to 5 second bolus intravenous injection.

Dosage in Previously Untreated Multiple Myeloma
BORT SPAL 3.5 is administered in combination with oral melphalan and oral prednisone for 9, six week treatment cycles as shown in Table 1. In Cycles 1 to 4, BORT SPAL 3.5 is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, BORT SPAL 3.5 is administered once weekly (Days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of BORT SPAL 3. 5.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice weekly BORT SPAL 3.5 (Cycles 1 to 4)											
Week	1				2	3	4		5		6
BORT SPAL 3.5 (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
Melphalan (9 mg/m2) (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period
Once weekly BORT SPAL 3.5 (Cycle 5 to 9 when used in combination with Melphalan and prednisone)											
Week	1				2	3	4		5		6
BORT SPAL 3.5 (1.3 mg/m^2)	Day 1	--	--		Day 8		Rest period	Day 22		Day 29		Rest period
Melphalan (9 mg/m2) (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period

Dose Modification Guidelines for BORT SPAL 3.5 when given in Combination with Melphalan and Prednisone
Prior to initiating any cycle of therapy with BORT SPAL 3.5 in combination with melphalan and prednisone:
- Platelet count should be at least 70 x 109/L and the absolute neutrophil count (ANC) should be at least 1.0 x 109/L
- Nonhematological toxicities should have resolved to Grade 1 or baseline

Table 2: Dose Modifications during Cycles of Combination BORT SPAL 3.5, Melphalan and Prednisone Therapy

Toxicity	**Dose modification or Delay**
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count is not above 30 × 10 9/L or ANC is not above 0.75 x 10^9/L on a BORT SPAL 3.5 dosing day (other than day 1)	Withhold BORT SPAL 3.5 dose
If several BORT SPAL 3.5 doses in consecutive cycles are withheld due to toxicity	Reduce BORT SPAL 3.5 dose 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 or higher non-hematological toxicities	Withhold BORT SPAL 3.5 therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, BORT SPAL 3.5 may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For BORT SPAL 3.5 related neuropathic pain and/or peripheral neuropathy, hold or modify BORT SPAL 3.5 as outlined

For information concerning melphalan and prednisone, see manufacturer's prescribing information.

Dose modifications guidelines for peripheral neuropathy are provided.

Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)

Combination therapy with dexamethasone

BORT SPAL 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection 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 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of BORT SPAL 3.5. Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the BORT SPAL 3.5 treatment cycle.

Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

BORT SPAL 3. 5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28-day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of BORT SPAL 3.5. Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the BORT SPAL 3.5 treatment cycle.

Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 3).

Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 3: Posology for BORT SPAL 3.5 combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

Bo+Dx	**Cycles 1 to 4**				
	Week	1	2	3	
	Bo (1.3 mg/m^2)	Day 1,4	Day 8,11[a]	Retest period	
	Dx 40mg	Day 1,2,3,4	Day 8,9,10,11	--	
Bo+Dx+T	**Cycle 1**				
Bo+Dx+T	Week	1	2	3	4
	Bo (1.3 mg/m^2)	Day 1,4	Day 8,11[a]	Retest period	Retest period
	T 50mg	Daily	Daily	-	-
	T 100mg[a]	-	-	Daily	Daily
	Dx 40mg	Day 1,2,3,4	Day 8,9,10,11	-	
	Cycles 2 [b]to 4[b]				
	Week	1	2	3	4
	Bo (1.3 mg/m^2)	Day 1,4	Day 8,11	Retest period	Retest period
	T 200mg[a]	Daily	Daily	Daily	Daily
	Dx 40mg	Day 1,2,3,4	Day 8,9,10,11	--	--

Bo=BORT SPAL; Dx=dexamethasone; T=thalidomide
a. Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.
b. Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients
For BORT SPAL 3.5 dosage adjustments, as described under **"Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma" and "Dose Modification Peripheral Neuropathy"** should be followed.
In addition, when BORT SPAL 3.5 is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the local package inserts.

Dosage in Previously Untreated Mantle Cell Lymphoma
BORT SPAL 3.5 (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (BoR-CAP) for 6 three week treatment cycles. BORT SPAL 3.5 is administered first followed by rituximab. BORT SPAL 3.5 is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period on Days 12 to 21. For patients with a response first documented at cycle 6, two additional BoRCAP cycles are recommended. At least 72 hours should elapse between consecutive doses of BORT SPAL 3.5.

Table 4: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma

Twice weekly BORT SPAL 3.5 (6, Three week cycles)*								
Week	1					2		
BORT SPAL 3.5 Vc (1.3 mg/m^2)	Day 1	--	--	Day 4	--	Day 8	Day 11	Retest period
Rituximab (375 mg/m Cyclophosp hamide (750 mg/m2) Doxorubicin (50 mg/m^2)	Day 1	--	--			--	--	Retest period
Prednisone (100 mg/m^2)	Day 1	Day 2	Day 3	Day 4	Day 5	--	-	Rest period

Dose Modification Guidelines for BORT SPAL 3.5 When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone
Prior to the first day of each cycle (other than Cycle 1):
Platelet count should be at least 100 x 10^9/L and absolute neutrophil count (ANC) should be at least 1.5 x 10^9/L
- Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline[a]

Interrupt BORT SPAL 3.5 treatment at the onset of any Grade 3 hematologic or non-hematological toxicities, excluding neuropathy special precautions for use. For dose adjustments, see Table 5 below.

Table 5 : Dose Modifications on Days 4, 8, and 11 during Cycles of Combination BORT SPAL 3.5,Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy

Toxicity	**Dose modification or Delay**
Hematological toxicity Grade 3 or higher neutropenia, or a platelet count not at or above 25 x10^9/L	Withhold BORT SPAL 3.5 therapy for up to 2 weeks until the patient has an ANC at or above 0.75 x 10^9/L and a platelet count at or 10^9/L above 25 x 10^9/L and a platelet count at or 10^9/L above 25 x 10^9/L. • If, after BORT SPAL 3.5 has been withheld, the toxicity does not resolve, discontinue BORT SPAL 3.5. • If toxicity resolves such that the patient has an ANC at or above 0.75 x 10^9/L and a platelet count at or above 25 x 10^9/L, BORT SPAL 3.5 dose should be reduced by 1dose 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 or higher non-hematological toxicities	Withhold BORT SPAL 3.5 therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, BORT SPAL 3.5 may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).

For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.

Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma
BORT SPAL 3.5 (1.3 mg/m2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period (Days 12 to 21). For extended therapy of more than eight cycles, BORT SPAL 3.5 may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of BORT SPAL 3.5 Patients with multiple myeloma who have previously responded to treatment with BORT SPAL 3.5 (either alone or in combination) and who have relapsed at least six months after their prior BORT SPAL 3.5 therapy may be started on BORT SPAL 3.5 at the last tolerated dose. Retreated patients are administered BORT SPAL 3.5 twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of BORT SPAL 3.5. BORT SPAL 3.5 may be administered either as a single agent or in combination with dexamethasone.

BORT SPAL 3.5 therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see Warning and Precautions). Once the symptoms of the toxicity have resolved, BORT SPAL 3.5 therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

For dose modifications guidelines for peripheral neuropathy, see Dose modifications for peripheral neuropathy below.

Dose Modifications for Peripheral Neuropathy

Starting BORT SPAL 3.5 subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with BORT SPAL 3.5 only after careful risk-benefit assessment Patients experiencing new or worsening peripheral neuropathy during BORT SPAL 3.5 therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience BORT SPAL 3.5-related neuropathic pain and/or peripheral neuropathy.

Recommended Dose Modification for BORT SPAL 3.5 related Neuropathic Pain and/or
Table 6 : Peripheral Sensory or Motor Neuropathy

Severity of peripheral neuropathy signs and symptoms	**Modifications of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesias) 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 BORT SPAL 3.5 to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL.***)	Withhold BORT SPAL 3.5 therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORT SPAL 3.5 at 0.7mg/m^2 once per week.
Grade 4 (life- threatening consequences; urgent intervention indicated)	Discontinue BORT SPAL 3.5

*Grading based on NCI Common Toxicity Criteria CTCAE v4.0.
**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

Special Populations
Patients with Renal Impairment
The pharmacokinetics of BORT SPAL 3.5 are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BORT SPAL 3.5 are not necessary for patients with renal insufficiency. Since dialysis may reduce BORT SPAL 3.5 concentrations, the drug should be administered after the dialysis procedure (see Pharmacokinetic Properties).

Patients with Hepatic Impairment
Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended BORT SPAL 3.5 dose. For patients with moderate or severe hepatic impairment, see Table 7 below, (also, see Pharmacokinetic Properties):

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

	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose in Multiple Myeloma and Relapsed Mantle Cell Lymphoma (1.3 mg/m^2 twice weekly)**
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x−1.5x ULN	Any	None
Moderate	> 1.5x−3x ULN	Any	Reduce BORT SPAL 3.5 to 0.7 mg/m^2 in the first cycle. Consider dose
Severe	> 3x ULN	Any	escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

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

Administration
BORT SPAL 3.5 is administered intravenously or subcutaneously. When administered intravenously, BORT SPAL 3.5 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.

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

If local injection site reactions occur following BORT SPAL 3.5 injection subcutaneously, a less concentrated BORT SPAL 3.5 solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously, or changed to IV injection.

i. Route of Administration
Bortezomib powder for solution for injection is administered via intravenous or subcutaneous injection.

j. Contraindications
BORT SPAL 3.5 is contraindicated in patients with hypersensitivity to bortezomib or any of the excipients.

k. Warnings and Precautions

Peripheral Neuropathy
Treatment with bortezomib is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy, with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

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

Bortezomib administered intravenously versus subcutaneously, the incidence of Grade ≥ 2 peripheral neuropathy events lower for the subcutaneous injection group and higher for the intravenous injection group. Grade ≥ 3 peripheral neuropathy occurred in less patients in the subcutaneous treatment group, compared with intravenous treatment group. The incidence of all grade peripheral neuropathy with bortezomib administered intravenously was lower.
Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule or route of administration to subcutaneous. Neuropathy has been managed with supportive care and other therapies.
Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving bortezomib in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered. In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Hypotension
The incidence of hypotension (postural, orthostatic, and hypotension NOS) was reported. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

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

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 BORTSPAL 3.5.

Pulmonary Disorders
There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving BORT SPAL 3.5. 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.

Daunorubicin and bortezomib with concomitant administration of high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Laboratory Tests
Complete blood counts (CBC) should be frequently monitored throughout treatment with BORT SPAL 3.5.

Thrombocytopenia/Neutropenia
BORT SPAL 3.5. is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. In the relapsed multiple myeloma study, the incidence of significant bleeding events (≥Grade 3) was similar on both the BORT SPAL 3.5. (4%) and dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of BORT SPAL 3.5.

Gastrointestinal Adverse Events
BORT SPAL 3.5 treatment can cause nausea, diarrhea, constipation, and vomiting (see Side Effects) sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving BORT SPAL 3.5 therapy may experience vomiting and/or diarrhea, 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.

Tumor Lysis Syndrome
Because BORT SPAL 3.5 is a cytotoxic agent and can rapidly kill malignant cells the complications of tumor lysis syndrome may occur. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Patients with Hepatic Impairment
Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with BORT SPAL 3.5 at reduced starting doses and closely monitored for toxicities. (See Recommended Dosage and Pharmacokinetic Properties)

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of PRES in patients receiving BORT SPAL 3.5. 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, bortezomib should be discontinued.

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

Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

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

Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

Drug Laboratory Test Interactions
None known

m. Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned below

General precautions
Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of bortezomib. Pregnant women should not handle this medicinal product. Use of gloves and other protective clothing to prevent skin contact is recommended.
Aseptic technique must be strictly observed throughout the handling of bortezomib, since it contains no preservative.
There have been fatal cases of inadvertent intrathecal administration of bortezomib. while BORT SPAL 3.5 is for intravenous or subcutaneous use. Bortezomib should not be administered intrathecally.
Instructions for reconstitution
Bortezomib must be reconstituted by a healthcare professional.
Intravenous injection
Each 10 ml vial of bortezomib must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.
Subcutaneous injection
Each 10 ml vial of bortezomib must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

n. Pregnancy and Lactation
Women of childbearing potential should avoid becoming pregnant while being treated with BORT SPAL 3.5.
No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If BORT SPAL 3.5 is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.
Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with BORT SPAL 3.5.

Nursing Mothers
It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BORT SPAL 3.5.,

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Sub Headings-Font Style: Times New Roman, Font Size: 7pt
Main Text-Font Style: Times New Roman, Font Size: 7pt

PRODUCT NAME	Bortezomib Powder for Solution for Injection 3.5 mg/vial	**ARTWORK NO.**	NA
COUNTRY	Malaysia	**SUPERSEDES NO**	NA
CUSTOMER	SP Accure Labs Pvt. Ltd.	**PANTONE SHADE NO'S**	Black
DIMENSIONS	615 x 330 mm ± 1 mm (L x H)	**VARNISHING/LAMINATE**	NA
SUBSTRATE	Maplitho Paper	**GRAMMAGE**	60 ± 10% GSM
MODE OF SUPPLY	Bundles		

women should be advised against breast feeding while being treated with BORT SPAL 3.5.

o. Side Effects

Serious adverse reactions uncommonly reported during treatment with BORT SPAL 3.5 include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

The most commonly reported adverse reactions during treatment with BORT SPAL 3.5 are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Adverse reactions occurs with Multiple Myeloma treated with BORT SPAL 3.5, and all post-marketing adverse reactions regardless of indication#

System Organ Class	Incidence	Adverse reaction
Infections infestations	Common	Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic#, Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia#
	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (inc thrombocytopenic purpura) #, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Angioedema#, Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality*
	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc dementia)*, Encephalopathy*, Posterior Reversible Encephalopathy Syndrome#, Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy*, Paralysis*, Paresis*, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia, Guillain-Barré syndrome#, Demyelinating polyneuropathy#
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion#, Blepharitis#, Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Lacrimationincreased, Eye discharge
	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy#, Different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc tinnitus)*,Hearing impaired (up to and inc deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade#, Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*
	Uncommon	Cerebrovascular accident#, Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage#, Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper-airway cough syndrome
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence
	Uncommon	Pancreatitis (inc chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic#, Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*
	Rare	Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis#, Stevens-Johnson syndrome#, Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer#, Acne*, Blister*, Pigmentation disorder*
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*,Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations*, Synovial cyst
Renal and urinary disorders	Common	Renal impairment*
	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Pain*, Malaise*
	Uncommon	General physical health deterioration*, Face oedema*, Injection site reaction*, Mucosal disorder*, Chest pain, Gait disturbance, Feeling cold, Extravasation*, Catheter related complication*, Change in thirst*, Chest discomfort, Feeling of body temperature change*, Injection site pain*
	Rare	Death (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia(inc hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*,C-reactive protein increased
	Rare	Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised ratio abnormal*, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology*, Urine analysis abnormal*
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

Adverse reactions occurs with Mantle Cell Lymphoma treated with BORT SPAL 3.5

Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*,Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

NOS=not otherwise specified
* Grouping of more than one MedDRA preferred term.
# Post-marketing adverse reaction regardless of indication

p. Symptoms and Treatment Of Overdose

Over dosage more than twice the recommended dose in patients has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for BORT SPAL 3.5 over dosage. In the event of an over dosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see Warning and Precautions and Recommended Dosage).

q. Effects on Ability to Drive and Use Machine

BORT SPAL 3.5 may cause tiredness, dizziness, fainting, or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms

r. Instructions for use

Administration Precautions

BORT SPAL 3.5 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. Local skin irritation was reported in 5% of patients, but extravasation of BORT SPAL 3.5 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 BORT SPAL 3.5.

BORT SPAL 3.5 is for IV and subcutaneous use only. **DO NOT ADMINISTER BORT SPAL 3.5 INTRATHECALLY.**

Reconstitution/Preparation for Intravenous and Subcutaneous Administration The contents of each vial should be reconstituted only with normal (0.9%) saline according to the following instructions based on route of administration

Table 8 Reconstitution/preparation intravenous and subcutaneous administration

	IV	SC
	3.5 mg bortezomib	3.5 mg bortezomib
Volume of diluent (0.9% Sodium Chloride) added to reconstitute one vial	3.5 mL	1.4 mL
Final Concentration after reconstitution (mg/mL)	1.0 mg/mL	2.5 mg/mL

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

Procedure for Proper Disposal

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

s. Storage Condition :

Do not store above 30°C.
Keep the vial in the outer carton in order to protect from light.

Reconstituted solution

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

t. Dosage forms and packaging available

The Bortezomib 3.5 mg powder for solution for injection is being primarily packed in 10 mL Tubular clear (Type-1 glass) 20 mm Collar flat bottom vial with 20 mm Grey bromobutyl single slotted lyo rubber stopper and sealed with 20 mm Aluminium flip-off seal of purple color button. The product packed in a carton along with package insert.

u. Shelf life

36 Months

v. Therapeutic code

L01XG01.

w. Name and address of manufacturer/ product registration holder

MANUFACTURED BY:

SP Accure Labs Pvt. Ltd.

Plot No.12, Biotech Park, Phase II, Lalgadi Malakpet(V), Shamirpet(M),
Medchal- Malkajgiri (Dist), 500 101, Telangana State. India

Product Registration Holder:
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74-3, Jalan Wangsa Delima 6,
KLSC Wangsa Maju,
53300 Kuala Lumpur, Malaysia.

x. Date of revision of PI

May 2023

VERP 3251