Alvocade®
Bortezomib

Powder for Solution for Injection

Read all of this leaflet carefully for complete instruction

1. INDICATIONS AND USAGE

1.1. Multiple Myeloma:

BORTEZOMIB is indicated for the treatment of patients with multiple myeloma.

1.2. Mantle Cell Lymphoma

BORTEZOMIB is indicated for the treatment of patients with mantle cell lymphoma.

2. DOSAGE AND ADMINISTRATION

2.1. General Dosing Guidelines

BORTEZOMIB is for intravenous or subcutaneous use only. BORTEZOMIB should not be administered by any other route.

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

The recommended starting dose of BORTEZOMIB is 1.3 mg/m^2. BORTEZOMIB may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL.

BORTEZOMIB retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with BORTEZOMIB and who have relapsed at least 6 months after completing prior BORTEZOMIB treatment. Treatment may be started at the

last tolerated dose.

When administered intravenously, BORTEZOMIB is administered as a 3 to 5 second bolus intravenous injection.

2.2. Dosage in Previously Untreated Multiple Myeloma

BORTEZOMIB is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1. In Cycles 1-4, BORTEZOMIB is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, BORTEZOMIB is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of BORTEZOMIB.

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

Twice Weekly BORTEZOMIB (Cycles 1-4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
BORTEZOMIB (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/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period
Once Weekly BORTEZOMIB (Cycles 5-9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
BORTEZOMIB (1.3 mg/m^2)	Day 1	--	--	--	Day 8	--	Rest period	Day 22	--	Day 29	--	Rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	Rest period	--	--	--	--	Rest period

2.3. Dose Modification Guidelines for BORTEZOMIB When Given in Combination with Melphalan and Prednisone

Prior to initiating any cycle of therapy with BORTEZOMIB in combination with melphalan and prednisone:

- Platelet count should be at least 70 × 10^9/L and the absolute neutrophil count (ANC) should be at least 1.0 × 10^9/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 2: Dose Modifications during Cycles of Combination BORTEZOMIB, 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 0.75×10^9 /L on a BORTEZOMIB dosing day (other than day 1)	Withhold BORTEZOMIB dose
If several BORTEZOMIB doses in consecutive cycles are withheld due to toxicity	Reduce BORTEZOMIB dose by 1 dose level (from 1.3 mg/m² to 1 mg/m² , or from 1 mg/m² to 0.7 mg/m²)
Grade 3 or higher non-hematological toxicities	Withhold BORTEZOMIB therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB may be reinitiated with one dose level reduction (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²). For BORTEZOMIB-related neuropathic pain and/or peripheral neuropathy, hold or modify BORTEZOMIB as outlined in Table 5.
For information concerning melphalan and prednisone, see manufacturer's prescribing information. Dose modifications guidelines for peripheral neuropathy are provided.	

2.4. Dosage in Previously Untreated Mantle Cell Lymphoma

BORTEZOMIB (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for six 3-week treatment cycles as shown in Table 3.

BORTEZOMIB is administered first followed by rituximab. BORTEZOMIB is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period on Days 12-21. For patients with a response first documented at cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of BORTEZOMIB.

Table 3: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma

Twice Weekly BORTEZOMIB (Six 3-Week Cycles)*								
Week	**1**					**2**		**3**
BORTEZOMIB (1.3 mg/m²)	Day 1	--	--	Day 4	--	Day 8	Day 11	Rest period
Rituximab (375 mg/m²) Cyclophosphamide (750 mg/m²) Doxorubicin (50 mg/m²)	Day 1	--	--	--	--	--	--	Rest period
Prednisone (100 mg/m²)	Day 1	Day 2	Day 3	Day 4	Day 5	--	--	Rest period

*Dosing may continue for 2 more cycles (for a total of 8 cycles) if response is first seen at cycle 6.

2.5. Dose Modification Guidelines for BORTEZOMIB 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 × 10^9/L and absolute neutrophil count (ANC) should be at least 1.5 × 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

Interrupt BORTEZOMIB treatment at the onset of any Grade 3 hematologic or non-hematological toxicities, excluding neuropathy. For dose adjustments, see Table 4 below.

Table 4: Dose Modifications on Days 4, 8, and 11 during Cycles of Combination BORTEZOMIB, 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 25×10^9 /L	Withhold BORTEZOMIB therapy for up to 2 weeks until the patient has an ANC at or above 0.75×10^9 /L and a platelet count at or above 25×10^9 /L. • If, after BORTEZOMIB has been withheld, the toxicity does not resolve, discontinue BORTEZOMIB. • If toxicity resolves such that the patient has an ANC at or above 0.75×10^9 /L and a platelet count at or above 25×10^9 /L, 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 or higher non-hematological toxicities	Withhold BORTEZOMIB therapy 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 or modify BORTEZOMIB as outlined in Table 5.
For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.	

2.6. Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

BORTEZOMIB (1.3 mg/m^2/dose) is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, BORTEZOMIB may be administered on the standard schedule or, for relapsed multiple myeloma, 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). At least 72 hours should elapse between consecutive doses of BORTEZOMIB.

Patients with multiple myeloma who have

previously responded to treatment with BORTEZOMIB (either alone or in combination) and who have relapsed at least 6 months after their prior BORTEZOMIB therapy may be started on BORTEZOMIB at the last tolerated dose. Retreated patients are administered BORTEZOMIB twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of 8 cycles. At least 72 hours should elapse between consecutive doses of BORTEZOMIB. BORTEZOMIB may be administered either as a single agent or in combination with dexamethasone.

BORTEZOMIB therapy should be withheld at the onset of any Grade 3 non-hematological

or Grade 4 hematological toxicities excluding neuropathy as discussed below. 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 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

2.7. Dose Modifications for Peripheral Neuropathy:

Starting BORTEZOMIB 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 BORTEZOMIB only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during BORTEZOMIB therapy may require a decrease in the dose and/or a less dose-intense schedule.

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 paresthesia) 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 mg/m^2
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 Terminology 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

2.8. Dosage in Patients with Hepatic Impairment:

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.

Table 6: Recommended Starting Dose Modification for BORTEZOMIB in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	Less than or equal to 1.0x ULN	More than ULN	None
	More than 1.0x-1.5x ULN	Any	None
Moderate	More than 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	More than 3x ULN	Any	

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

2.9. Preparation and Administration Precautions:

The drug quantity contained in one 3.5-mg vial, may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following BORTEZOMIB administration subcutaneously, a less concentrated BORTEZOMIB solution (1 mg/mL instead of 2.5 mg/mL) may be administered

subcutaneously.

Alternatively, the intravenous route of administration should be considered.

BORTEZOMIB is an antineoplastic. Procedures for proper handling and disposal should be considered.

2.10. Reconstitution/ Preparation for Intravenous Administration:

Proper aseptic technique should be used. Reconstitute **only with 0.9% sodium chloride**. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% sodium chloride are used to reconstitute the product for

the different routes of administration. The reconstituted concentration of BORTEZOMIB for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of BORTEZOMIB for intravenous administration (1 mg/mL).

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

For each single-use vial of BORTEZOMIB reconstitute with the following volume of 0.9% sodium chloride based on route of administration and dosage.

Table 7: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of administration	Bortezomib (mg/vial)	Diluent (%0.9 Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL
Intravenous	1 mg	1 mL	1 mg/mL

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total

volume (mL) of reconstituted BORTEZOMIB to be administered:

- **Intravenous Administration [1 mg/mL concentration]**

$$\frac{(\text{BORTEZOMIB Dose (mg/m}^2) \times \text{Patient BSA (m}^2)}{1 \text{ mg/mL}} =$$

Total BORTEZOMIB Volume (mL) to be Administered

- **Subcutaneous Administration [2.5 mg/mL concentration]**

$$\frac{\text{BORTEZOMIB Dose (mg/m}^2) \times \text{Patient BSA (m}^2)}{2.5\text{mg/mL}} =$$

Total BORTEZOMIB Volume (mL) to be Administered

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.

2.11. Stability:

Unopened vials of BORTEZOMIB are stable until the date indicated on the package when stored in the original package protected from light.

BORTEZOMIB contains no antimicrobial preservative. Reconstituted BORTEZOMIB should be administered immediately after preparation because of microbiological concerns. If not

used immediately, in-use storage times and conditions prior to use are the responsibility of user.

3. DOSAGE FORMS AND STRENGTHS

ALVOCADE®, BORTEZOMIB for injection, is a white to off-white lyophilized powder available in sterile single-use vials containing 1 mg or 3.5 mg BORTEZOMIB.

4. CONTRAINDICATIONS

BORTEZOMIB is contraindicated in patients with hypersensitivity (not including local reactions) to Bortezomib, boron, or mannitol.

Reactions have included anaphylactic reactions.

BORTEZOMIB is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of BORTEZOMIB.

5. WARNINGS AND PRECAUTIONS:

5.1. Peripheral Neuropathy: BORTEZOMIB treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience

worsening peripheral neuropathy (including ≥ Grade 3) during treatment with BORTEZOMIB. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy during BORTEZOMIB therapy may require a decrease in the dose and/or a less dose-intense schedule.

5.2. Hypotension: The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. 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.

5.3. Cardiac Toxicity: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during BORTEZOMIB therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk

factors for, or existing heart disease should be closely monitored.

5.4. Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, and lung infiltration have occurred in patients receiving BORTEZOMIB. Some of these events have been fatal. There have been reports of pulmonary hypertension associated with BORTEZOMIB administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, consider interrupting BORTEZOMIB until

a prompt and comprehensive diagnostic evaluation is conducted.

5.5. Posterior Reversible Encephalopathy Syndrome (PRES): Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred 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.

5.6. Gastrointestinal Toxicity: BORTEZOMIB treatment can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt BORTEZOMIB for severe symptoms.

5.7. Thrombocytopenia/Neutropenia:

BORTEZOMIB 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. Monitor complete blood counts (CBC) frequently during treatment with BORTEZOMIB. Measure platelet counts prior to each dose of BORTEZOMIB. Adjust dose schedule for thrombocytopenia. Gastrointestinal and intracerebral hemorrhage has occurred during thrombocytopenia in association with BORTEZOMIB. Support with transfusions and supportive care, according to published guidelines.

5.8. Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with BORTEZOMIB therapy. Patients at risk of tumor lysis syndrome

are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

5.9. Hepatic Toxicity: Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions.

Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt BORTEZOMIB therapy to assess reversibility. There is limited re-challenge information in these patients.

5.10. Embryo-fetal Risk: Women of reproductive potential should avoid becoming pregnant while being treated with BORTEZOMIB**.**

Advise females and males of reproductive potential that they must use contraception during treatment with BORTEZOMIB and for 2 months following treatment. If BORTEZOMIB is used during pregnancy or if the patient becomes pregnant during BORTEZOMIB treatment, the patient should be apprised of the potential risk to the fetus.

6. ADVERSE REACTIONS

Adverse reactions and incidences reported are associated with monotherapy.

>10%:

Central nervous system: Fatigue (7% to 52%),

fever (8% to 35%), headache (10% to 19%), dizziness (10% to 18%; excludes vertigo)

Dermatologic: Rash (12% to 23%)

Gastrointestinal: Diarrhea (19% to 52%), nausea (16% to 52%), constipation (25% to 30%), vomiting (9% to 29%), anorexia (14% to 21%), abdominal pain (11%), appetite decreased (11%)

Hematologic: Thrombocytopenia (30% to 34%; grade 3: 5% to 24%; grade 4: 3% to 7%; nadir: Day 11; recovery: By day 21), neutropenia (10% to 27%; grade 3: 8% to 14%; grade 4: 2% to 4%; nadir: Day 11; recovery: By day 21), anemia (19% to 23%; grade 3: 4% to 6%; grade 4: <1%), leukopenia (18% to 20%; grade 3: 5%;

grade 4: 1%)

Neuromuscular & skeletal: Peripheral neuropathy (SubQ 37%; I.V. 35% to 54%; grade ≥2: 24% to 39%; grade 3: SubQ 5%; I.V. 7% to 14%; grade 4: 1%), neuralgia (23%), paresthesia (7% to 19%), weakness (7% to 16%)

Respiratory: Dyspnea (11%)

1% to 10%:

Cardiovascular: Cardiac disorder (treatment emergent; 8%), hypotension (8%; grades 3/4: 2%), heart failure (≤1%; includes acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock)

Endocrine & metabolic: Dehydration (2%)

Hematologic: Bleeding (≥grade 3: 2%)

Local: Injection site irritation (SC 6%; I.V. 5%)

Respiratory: Pneumonia (1%)

Miscellaneous: Herpes zoster (1% to 2%)

<1% (Limited to important or life-threatening):

Acute diffuse infiltrative pulmonary disease, acute respiratory distress syndrome (ARDS), alkaline phosphatase increased, amyloidosis, anaphylaxis, angina pectoris, angioedema, ascites, aspergillosis, atelectasis, atrial fibrillation exacerbation, atrial flutter, AV block, bacteremia, blindness, bone pain, bradycardia, cardiac amyloidosis, cardiac arrest, cardiac tamponade, cardiopulmonary arrest, catheter-related infection, cerebral hemorrhage, cerebrovascular accident, coma, conjunctival infection/irritation, cranial palsy, deep vein thrombosis, diplopia, disseminated intravascular coagulation (DIC), duodenitis (hemorrhagic), dysarthria, dysautonomia, dysgeusia, dyspepsia, dysphagia, edema, embolism, encephalopathy, epistaxis, fecal impaction, gastritis (hemorrhagic), gastroenteritis, gastroesophageal reflux, GGT increased, glomerular nephritis, hearing impairment, hematemesis, hematuria, hemoptysis,

hemorrhagic cystitis, hepatic failure, hepatic hemorrhage, hepatitis, hepatocellular damage, herpes meningoencephalitis, hyperbilirubinemia, hyper-/hypoglycemia, hyper-/hypokalemia, hyper-/hyponatremia, hypersensitivity, hyperuricemia, hypocalcemia, hypoxia, ileus, interstitial pneumonia, intestinal perforation, intracerebral hemorrhage, ischemic colitis, ischemic stroke, laryngeal edema, left ventricular ejection fraction decreased, leukocytoclastic vasculitis, limb pain, listeriosis, lymphopenia, melena, MI, myalgia, myocardial ischemia, nasopharyngitis, neutropenic fever, ophthalmic herpes, optic neuritis, oral candidiasis, oral mucosal petechiae, pancreatitis, paralytic ileus, pericardial effusion,

pericarditis, peritonitis, phlebitis, pleural effusion, pneumonitis, portal vein thrombosis, posterior reversible encephalopathy syndrome (PRES), proliferative glomerular nephritis, pruritus, psychosis, pulmonary embolism, pulmonary hypertension, pulmonary infiltrate, QT_c prolongation, renal failure, respiratory failure, respiratory insufficiency, respiratory tract infection, seizure, sepsis, septic shock, SIADH, sinus arrest, sinusitis, spinal cord compression, Stevens-Johnson syndrome, stomatitis, stroke (hemorrhagic), subarachnoid hemorrhage, subdural hematoma, suicidal ideation, Sweet's syndrome (acute febrile neutrophilic dermatosis), syncope, tachycardia,

torsade de pointes, toxic epidermal necrolysis, toxoplasmosis, transaminases increased, transient ischemic attack, tumor lysis syndrome, ventricular tachycardia, weight loss

7. DRUG INTERACTIONS

7.1. Risk C (Monitor therapy):

Aripiprazole, Aripiprazole, CYP2C19 Substrates, Dasatinib, CYP3A4 Inhibitors (Strong), Deferasirox, Ivacaftor, Peginterferon Alfa-2b, Tocilizumab, CYP3A4 Inhibitors (Moderate)

7.2. Risk D (Consider therapy modification):

Ascorbic Acid, Lomitapide, Mifepristone, Multivitamins/Minerals (with ADEK, Folate,

Iron), Citalopram, CYP3A4 Inducers (Strong)

7.3. Risk X (Avoid Combination):

Clopidogrel, Clozapine, CYP3A4 Inducers (Strong), Green Tea, Pimozide, St Johns Wort

Nutrition/Herb Interactions:

Food: Avoid grapefruit juice (may increase BORTEZOMIB levels).

Herb/Nutraceutical: Avoid St John's wort (may decrease BORTEZOMIB levels). Avoid green tea and green tea extracts (may diminish the therapeutic effect of BORTEZOMIB). Avoid ascorbic acid supplements, including multivitamins containing ascorbic acid (may diminish BORTEZOMIB activity) during treatment, especially 12 hours before and

after BORTEZOMIB treatment.

Avoid grapefruit juice (may increase bortezomib levels).

8. USE IN SPECIAL POPULATIONS

8.1. Pregnancy:

Pregnancy Risk Factor: **D**

Adverse effects (fetal loss and decreased fetal weight) were observed in animal reproduction studies at doses less than the equivalent human dose (based on BSA). Women of reproductive potential should avoid becoming pregnant and should use effective contraception during treatment.

8.2. Nursing Mothers:

Lactation Excretion in breast milk unknown/ not recommended.

Breast-Feeding Considerations: the decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother.

8.3. Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, BORTEZOMIB can cause fetal harm when administered to a pregnant woman.

Verify the pregnancy status of females of

reproductive potential prior to initiating BORTEZOMIB treatment.

Advise patients of reproductive potential to use effective contraception during treatment with BORTEZOMIB and for at least 2 months after treatment.

Based on the mechanism of action and findings in animals, BORTEZOMIB may have an effect on either male or female fertility.

8.4. Pediatric Use

The effectiveness of BORTEZOMIB in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established.

8.5. Geriatric Use

No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving BORTEZOMIB; but greater sensitivity of some older individuals cannot be ruled out.

8.6. Patients with Renal Impairment

The pharmacokinetics of BORTEZOMIB are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BORTEZOMIB are not necessary for patients with renal insufficiency. Since dialysis may reduce BORTEZOMIB concentrations, BORTEZOMIB should be administered after the dialysis procedure.

8.7. Patients with Hepatic Impairment

The exposure of BORTEZOMIB is increased in patients with moderate (bilirubin ≥ 1.5 – 3× ULN) and severe (bilirubin > 3 × ULN) hepatic impairment. Starting dose should be reduced in those patients.

8.8. Patients with Diabetes

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving BORTEZOMIB treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medication.

9. OVERDOSAGE

There is no known specific antidote for BORTEZOMIB overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

10. DESCRIPTION

ALVOCADE® for Injection contains Bortezomib

which is an antineoplastic agent. BORTEZOMIB is a modified dipeptidyl boronic acid.

ALVOCADE® is available for Intravenous injection use in 1 mg and 3.5 mg sterile lyophilized powder in single-use vials.

The 3.5 mg vial can also be administered subcutaneously.

Each 1 and 3.5 mg vials also contains mannitol as Inactive ingredient: 10 mg mannitol for each 1-mg vial and 35 mg mannitol for each 3.5-mg vial. The product is provided as a mannitol boronic ester which, in reconstituted form, 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.

11. CLINICAL PHARMACOLOGY

11.1. Mechanism of Action:

Bortezomib inhibits proteasomes, enzyme complexes which regulate protein homeostasis within the cell. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis.

11.2. Pharmacokinetic:

Distribution: V_{dss}: 498-1884 L/m^2; distributes widely to peripheral tissues

Protein binding: ~83%

Metabolism: Hepatic primarily via CYP2C19 and 3A4 and to a lesser extent CYP1A2; forms metabolites (inactive) via deboronization followed by hydroxylation

Half-life elimination: Single dose: I.V.: 9-15 hours; multiple dosing: 1 mg/m^2: 40-193 hours; 1.3 mg/m^2: 76-108 hours

12. HOW SUPPLIED / STORAGE AND HANDLING

12.1. How supplied:

ALVOCADE® (Bortezomib) for Injection is supplied as individually cartoned 10 mL vials containing 1 or 3.5 mg Bortezomib as a white

to off-white cake or powder.

12.2. Storage Conditions:

Unopened vials may be stored at controlled room temperature between 15 to 30°C (59 to 86°F). Retain in original package to protect from light.

12.3. Handling and Disposal:

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact. Several guidelines on this subject have been published. References for some of these guidelines are as below:

- **NIOSH Alert:** Preventing occupational exposures

to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

- **OSHA Technical Manual,** TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
- **American Society of Health-System Pharmacists.** (2006) ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2006; 63:1172-1193.

Disclaimer: This leaflet was last approved in May 2018. This content should not be considered complete and may not include all the information needed to use Bortezomib for injection safely and effectively.

To access the latest revision of this prescribing information, please visit our website: www.nanoalvand.com

Last revision: May 2018

Manufacturing Authorization Holder & Manufacturing Site:
Nanoalvand Co.
Tehran, IRAN

Pharmaceutical Incubation Center, Avicenna Tech. Park of Tehran University of Medical Sciences, No. 1462, North Kargar Ave., Tehran, Iran.
P.O.Box: 1439955991
Tel: +9821-88020579
Fax: +9821-88020597
E-mail: info@nanoalvand.com
URL: www.nanoalvand.com