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Press Release

Hikma launches Bortezomib for Injection

London, 20 September, 2022 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Bortezomib for Injection, 3.5mg, in the US. The drug is indicated for the treatment of adult patients with multiple myeloma and mantle cell lymphoma.

According to IQVIA, US sales of Bortezomib Injection, 3.5mg, were approximately $1 billion in the 12 months ending June 2022.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the United States (US), the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,700 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

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Important Safety Information for Bortezomib Injection, 3.5mg:

CONTRAINDICATIONS

Bortezomib for injection is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions *[see Adverse Reactions (6.1)]*.

Bortezomib for injection is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of bortezomib for injection.

WARNINGS & PRECAUTIONS

- **Peripheral Neuropathy:** Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported.
- **Hypotension:** The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8% *[see Adverse Reactions (6.1)]*. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension.
- **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 *[see Adverse Reactions (6.1)]*.
- **Pulmonary Toxicity:** Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, 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.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving bortezomib.
- **Gastrointestinal Toxicity:** Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting *[see Adverse Reactions (6.1)]* sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur.
- **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.
- **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.
- **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.
- **Thrombotic Microangiopathy:** Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received bortezomib.
- **Embryo-Fetal Toxicity:** Based on the mechanism of action and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman.

ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed in other sections of the labeling:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Cardiac Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.5)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.6)]*
- Thrombocytopenia/Neutropenia *[see Warnings and Precautions (5.7)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.8)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.9)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (5.10)]*

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Most Common Adverse Drug Reactions
Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia. (6.1).

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma
Table 9 of the package insert describes safety data from 340 patients with previously untreated multiple myeloma who received bortezomib (1.3 mg/m^2) administered intravenously in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective randomized study.

The safety profile of bortezomib in combination with melphalan/prednisone is consistent with the known safety profiles of both bortezomib and melphalan/prednisone.

Relapsed Multiple Myeloma Randomized Study of Bortezomib vs Dexamethasone
The safety data described in *Table 10* of the package insert reflect exposure to either bortezomib (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. Bortezomib was administered intravenously at doses of 1.3 mg/m^2 twice weekly for two out of three weeks (21 day cycle). After eight, 21 day cycles patients continued therapy for three, 35 day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (nine months) with a median duration of six cycles (4.1 months).

Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma
In the Phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged bortezomib treatment. These patients were treated for a total of 5.3 to 23 months, including time on bortezomib in the prior bortezomib study *[see Clinical Studies (14.1)]*.

Safety Experience from the Phase 3 Open-Label Study of Bortezomib Subcutaneous vs Intravenous in Relapsed Multiple Myeloma
The safety and efficacy of bortezomib administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of bortezomib subcutaneous vs intravenous in 222 patients with relapsed multiple myeloma. The safety data described in *Table 11* of the package insert reflect exposure to either bortezomib subcutaneous (N=147) or bortezomib intravenous (N=74) *[see Clinical Studies (14.1)]*.

Safety Experience from the Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma
Table 12 of the package insert describes safety data from 240 patients with previously untreated mantle cell lymphoma who received bortezomib (1.3 mg/m^2) administered intravenously in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.

Integrated Summary of Safety (Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma)
Safety data from Phase 2 and 3 studies of single agent bortezomib 1.3 mg/m^2/dose twice weekly for two weeks followed by a ten day rest period in 1,163 patients with previously-treated multiple myeloma (N=1,008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 open-label study of bortezomib subcutaneous vs intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of bortezomib was similar in patients with multiple myeloma and mantle cell lymphoma.

Description of Selected Adverse Reactions from the Integrated Phase 2 and 3 Relapsed Multiple Myeloma and Phase 2 Relapsed Mantle Cell Lymphoma Studies
Refer to the package insert for description of selected adverse reactions regarding *Gastrointestinal Toxicity, Thrombocytopenia, Peripheral Neuropathy, Hypotension, Neutropenia, Asthenic Conditions (Fatigue, Malaise, Weakness, Asthenia), Pyrexia, and Herpes Virus Infection.*

Retreatment in Relapsed Multiple Myeloma

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A single-arm trial was conducted in 130 patients with relapsed multiple myeloma to determine the efficacy and safety of retreatment with intravenous bortezomib. The safety profile of patients in this trial is consistent with the known safety profile of bortezomib-treated patients with relapsed multiple myeloma as demonstrated in *Table 10*, *Table 11*, and *Table 13* of the package insert; no cumulative toxicities were observed upon retreatment.

Additional Adverse Reactions from Clinical Studies
The following clinically important serious adverse reactions that are not described above have been reported in clinical trials in patients treated with bortezomib administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and Lymphatic System Disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia
Cardiac Disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia
Ear and Labyrinth Disorders: Hearing impaired, vertigo
Eye Disorders: Diplopia and blurred vision, conjunctival infection, irritation
Gastrointestinal Disorders: Abdominal pain, ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux
General Disorders and Administration Site Conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis
Hepatobiliary Disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure
Immune System Disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema
Infections and Infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheterrelated infection
Injury, Poisoning and Procedural Complications: Catheter-related complication, skeletal fracture, subdural hematoma
Investigations: Weight decreased
Metabolism and Nutrition Disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia
Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity
Nervous System Disorders: Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack
Psychiatric Disorders: Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation
Renal and Urinary Disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative
Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, cough, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis,
hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension
Skin and Subcutaneous Tissue Disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus
Vascular Disorders: Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, hypertension, peripheral embolism, pulmonary embolism, pulmonary hypertension

Postmarketing Experience
The following adverse reactions have been identified from the worldwide postmarketing experience with 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:

Cardiac Disorders: Cardiac tamponade
Ear and Labyrinth Disorders: Deafness bilateral
Eye Disorders: Optic neuropathy, blindness, chalazion/blepharitis

Gastrointestinal Disorders: Ischemic colitis
Infections and Infestations: Progressive multifocal leukoencephalopathy (PML), ophthalmic herpes, herpes meningoencephalitis
Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES, formerly RPLS), Guillain-Barre syndrome, demyelinating polyneuropathy
Respiratory, Thoracic and Mediastinal Disorders: Acute diffuse infiltrative pulmonary disease
Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute febrile neutrophilic dermatosis (Sweet's syndrome)

DRUG INTERACTIONS

Effects of Other Drugs on Bortezomib

Strong CYP3A4 Inducers

Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may decrease bortezomib efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors

Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may increase the risk of bortezomib toxicities. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

Drugs Without Clinically Significant Interactions with Bortezomib

No clinically significant drug interactions have been observed when bortezomib was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and findings in animals, bortezomib can cause fetal harm when administered to a pregnant woman. There are no studies with the use of bortezomib in pregnant women to inform drug-associated risks.

Lactation

Risk Summary

There are no data on the presence of bortezomib or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from bortezomib is unknown, advise nursing women not to breastfeed during treatment with bortezomib and for two months after treatment.

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. Advise females of reproductive potential to use effective contraception during treatment with bortezomib and for seven months after the last dose. Males with female partners of reproductive potential should use effective contraception during treatment with bortezomib and for four months after the last dose. Based on the mechanism of action and findings in animals, bortezomib may have an effect on either male or female fertility.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

The activity and safety of bortezomib in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, nonrandomized cooperative group trial.

No new safety concerns were observed when bortezomib was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without bortezomib. The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the bortezomib arm and 120 (36%) on the dexamethasone arm. 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.

Renal Impairment
No starting dosage adjustment of bortezomib is recommended for patients with renal impairment. In patients requiring dialysis, bortezomib should be administered after the dialysis procedure.

Hepatic Impairment
No starting dosage adjustment of bortezomib is recommended for patients with mild hepatic impairment. The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment.

Patients with Diabetes
During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. 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.

DOSAGE AND ADMINISTRATION

Important Dosing Guidelines
Bortezomib for injection is for intravenous or subcutaneous use only. Do not administer bortezomib for injection 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 bortezomib for injection is 1.3 mg/m^2. Bortezomib for injection is administered intravenously at a concentration of 1 mg per mL, or subcutaneously at a concentration of 2.5 mg per mL.

Bortezomib for injection retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with bortezomib for injection and who have relapsed at least six months after completing prior bortezomib for injection treatment. Treatment may be started at the last tolerated dose.

When administered intravenously, administer bortezomib for injection as a 3 to 5 second bolus intravenous injection.

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

Dose Modification Guidelines for Bortezomib for Injection When Given in Combination with Melphalan and Prednisone
Prior to initiating any cycle of therapy with bortezomib for injection in combination with melphalan and prednisone:
- Platelet count should be at least 70 × 109/L and the absolute neutrophil count (ANC) should be at least 1 × 109/L
- Nonhematological toxicities should have resolved to Grade 1 or baseline

Refer to *Table 2* of the package insert for Dose Modifications During Cycles of Combination Bortezomib for Injection, Melphalan and Prednisone Therapy. For information concerning melphalan and prednisone, see manufacturer's prescribing information. Dose modifications guidelines for peripheral neuropathy are provided.

Dosage in Previously Untreated Mantle Cell Lymphoma

Bortezomib for injection (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6, three week treatment cycles as shown in *Table 3* of the package insert.

Bortezomib for injection is administered first followed by rituximab. Bortezomib for injection 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 VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of bortezomib for injection.

Dose Modification Guidelines for Bortezomib for Injection 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 × 109/L and absolute neutrophil count (ANC) should be at least 1.5 × 109/L
- Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
- Nonhematologic toxicity should have recovered to Grade 1 or baseline

Interrupt bortezomib for injection treatment at the onset of any Grade 3 hematologic or nonhematological toxicities, excluding neuropathy *[see Table 5 of the package insert]*. For dose adjustments, see *Table 4* of the package insert.

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
Bortezomib for injection (1.3 mg/m^2/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, bortezomib for injection 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) *[see Clinical Studies (14)]*. At least 72 hours should elapse between consecutive doses of bortezomib for injection.

Patients with multiple myeloma who have previously responded to treatment with bortezomib for injection (either alone or in combination) and who have relapsed at least six months after their prior bortezomib for injection therapy may be started on bortezomib for injection at the last tolerated dose. Retreated patients are administered bortezomib for injection 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 bortezomib for injection. Bortezomib for injection may be administered either as a single agent or in combination with dexamethasone *[see Clinical Studies (14.1)]*.

Bortezomib for injection therapy should be withheld at the onset of any Grade 3 nonhematological or Grade 4 hematological toxicities excluding neuropathy as discussed below *[see Warnings and Precautions (5)]*. Once the symptoms of the toxicity have resolved, bortezomib for injection 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).

Dose Modifications for Peripheral Neuropathy
Starting bortezomib for injection 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 for injection only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during bortezomib for injection 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 bortezomib for injection-related neuropathic pain and/or peripheral neuropathy, see *Table 5* of the package insert.

Dosage in Patients with Hepatic Impairment
Do not adjust the starting dose for patients with mild hepatic impairment.

Start patients with moderate or severe hepatic impairment at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and consider subsequent dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 based on patient tolerance *(see Table 6 of the package insert) [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Administration Precautions
The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose *[see Dosage and Administration (2.10)]*.

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 for injection administration subcutaneously, a less concentrated bortezomib for injection solution (1 mg per mL instead of 2.5 mg per mL) may be administered subcutaneously *[see Dosage and Administration (2.10)]*. Alternatively, consider use of the intravenous route of administration *[see Dosage and Administration (2.10)]*.

Bortezomib for injection is a hazardous drug. Follow applicable special handling and disposal procedures.

Reconstitution/Preparation for Intravenous and Subcutaneous Administration
Use proper aseptic technique. 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 per mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg per mL). **Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered** *[see Dosage and Administration (2.9)]*.

For each 3.5 mg single-dose vial of bortezomib, reconstitute with the following volume of 0.9% sodium chloride based on route of administration (*Table 7 of the package insert*).

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the equations in the package insert to calculate the total volume (mL) of reconstituted bortezomib for injection to be administered.

Stickers that indicate the route of administration are provided with each bortezomib for injection vial. These stickers should be placed directly on the syringe of bortezomib for injection once bortezomib for injection is prepared to help alert practitioners of the correct route of administration for bortezomib for injection.

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.

Stability
Unopened vials of bortezomib for injection are stable until the date indicated on the package when stored in the original package protected from light.

Bortezomib for injection contains no antimicrobial preservative. Administer reconstituted bortezomib for injection within eight hours of preparation. When reconstituted as directed, bortezomib for injection may be stored at 25oC (77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to eight hours in a syringe; however, total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

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 (5.2) and thrombocytopenia (5.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as two times the recommended clinical dose on a mg/m2 basis were associated with increases in heart rate, decreases in contractility,

hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at one hour postadministration, with progression to death in 12 to 14 hours following drug administration.

INDICATIONS AND USAGE

Multiple Myeloma

Bortezomib for injection is indicated for the treatment of adult patients with multiple myeloma.

Mantle Cell Lymphoma

Bortezomib for injection is indicated for the treatment of adult patients with mantle cell lymphoma.

HOW SUPPLIED/STORAGE AND HANDLING

Bortezomib for injection is supplied as individually cartoned 8 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

NDC 0143-9098-01 3.5 mg single-dose vial

Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Retain in original package to protect from light.

Follow guidelines for handling and disposal for hazardous drugs, including the use of gloves and other protective clothing to prevent skin contact.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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