Bortezomib

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Drug name: Bortezomib, formerly PS-341, also is known as Velcade™ (Millennium Pharmaceuticals, Inc., Cambridge, MA).

Classification: Bortezomib is a first-in-class proteasome inhibitor. The proteasome helps to control the level of many regulatory proteins involved in cell replication and survival.

Indications: Relapsed and refractory multiple myeloma.

Action: Bortezomib induces cancer cell apoptosis; limits tumor survival, growth, spread, and angiogenesis; affects cellular signals involved in resistance to standard chemotherapies; and affects the ability of myeloma cells to interact with bone marrow microenvironment.

Excretion: Elimination of metabolites is both renal and hepatic. Less than 10% of bortezomib is eliminated unchanged in urine. No pharmacokinetic data are available for patients with impaired hepatic function or those with renal insufficiency.

Half-life: After bolus injection, bortezomib is distributed rapidly into tissues from plasma ($t\frac{1}{2}\alpha < 10$ minutes). Tissue distribution is wide, except in the central nervous system and various regions of the eye. The estimated terminal elimination half-life of bortezomib ranges from 5–15 hours.

Adverse reactions: In two pivotal phase II clinical trials (N = 256), the most commonly reported adverse events were nausea (62%), fatigue (54%), diarrhea (48%), constipation (41%), thrombocytopenia (41%), pyrexia (36%), overall peripheral neuropathy (35%), vomiting (34%), and anorexia (30%).

Interactions: No formal drug interaction studies have been performed with bortezomib. Patients who concurrently are taking medications that can lead to myelosuppression (e.g., melphalan) should be monitored closely and careful risk and benefit assessment should be done for those medications. In vitro studies indicate that bortezomib is a poor inhibitor of cytochrome P450 (CYP) 3A4, 1A2, 2C9, 2C19, and 2D6. Patients who are receiving bortezomib concomitantly with a drug that is an inhibitor or inducer of CYP3A4 (inhibitors include amiodarone, cimetidine, grapefruit juice, azoles, and erythromycin; inducers include barbiturates, carbamazepine, and dexamethasone) should be monitored closely for either toxicities or reduced efficacy. [*Note.* This list is not inclusive of all agents that may inhibit or induce CYP3A4.] In clinical trials, hypoglycemia and hyperglycemia were reported in patients with diabetes receiving antidiabetic agents. Patients taking oral antidiabetic drugs may require dose adjustments while receiving bortezomib. Because of thrombocytopenic effects associated with bortezomib, patients may have increased risk of bleeding if they are receiving concomitant anticoagulants, nonsteroidal anti-inflammatory drugs, and thrombolytic agents. Because bortezomib is an antineoplastic agent, growth factors such as granulocyte–colony-stimulating factor (filgrastim) or granulocyte macrophage–colony-stimulating factor are contraindicated within 24 hours of treatment.

Dosage and administration: Bortezomib is administered as a three- to five-second IV push. It can be injected directly into a peripheral line, central line catheter, or an infusion port followed by standard saline flush to ensure administration of the full dose. Bortezomib is administered twice a week for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12–21) at 1.3 mg/m^2 dose in a 21-day cycle regimen. At least a 72-hour rest period between doses must be observed to allow restoration of normal proteasome function.

Dilution and reconstitution: Bortezomib is reconstituted with 3.5 ml of normal saline (0.9% sodium chloride solution). Once reconstituted, the drug should be administered within eight hours of preparation and can be stored in the syringe for up to three hours. Reconstituted bortezomib does not need to be protected from indoor light and can be stored at 25°C (77°F). Excursions are permitted from 15°C–30°C (59°F–86°F). Unopened vials are stored at the same temperature (25°C [77°F]) with the same excursions permitted, but they should be retained in their original package to protect them from light.

Availability: Bortezomib comes in an individually packaged 10 ml single-dose vial containing 3.5 mg bortezomib as a lyophilized white to off-white cake or powder. Once reconstituted with 3.5 ml normal saline, each ml contains 1 mg of bortezomib.

Handling precautions: Handling and preparation precautions include reconstituting bortezomib in a vertical flow chemotherapy hood, using gloves and other protective clothing to prevent skin contact, and using proper aseptic technique. Bortezomib is an antineoplastic but not a vesicant.

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