Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	November 6, 2018
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Product Name:	Velcade® (bortezomib)
Pediatric Labeling Approval Date:	September 14, 2015
Application Type/Number:	NDA 021602
Applicant/Sponsor:	Millennium Pharmaceuticals
OSE RCM #:	2018-1423

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Velcade® (bortezomib) in pediatric patients through age 16. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on the U.S. serious, unlabeled adverse events associated with bortezomib in pediatric patients.

The FDA approved bortezomib on May 13, 2003, and it is indicated for treatment of patients with multiple myeloma or mantle cell lymphoma. Bortezomib is not approved for a pediatric indication because no clinical benefit was demonstrated in the clinical trial in 2015.

Of the pediatric reports reviewed, there were no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly attributable to bortezomib. Although we reviewed all U.S. serious FAERS reports in pediatric patients (ages 0 to <17 years) received from September 14, 2015 (approval of pediatric labeling date) through July 2, 2018, only 15 cases were included in our case series. We excluded reports that were either duplicates, previously reviewed for the pediatric labeling change approval, or where a temporal relationship to bortezomib could not be determined. The majority of excluded reports included labeled adverse events for bortezomib. Most of these events were also attributable to concomitant medications or underlying malignancy.

These 15 cases described unlabeled adverse events. The cases either lacked sufficient details such as dechallenge or rechallenge information to determine causality or were labeled events with concomitant medications.

DPV did not identify any pediatric safety concerns for bortezomib at this time. DPV recommends no regulatory action and will continue to monitor all adverse events associated with the use of bortezomib.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Velcade® (bortezomib) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on the U.S. serious, unlabeled adverse events associated with bortezomib in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Bortezomib inhibits the chymotrypsin-like activity of the 26S proteasome and was initially approved on May 13, 2003 for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.[1] Bortezomib was initially approved for intravenous injection (IV) use only.[1] Subsequently, bortezomib was approved for the following indications and routes of administration in the adult population, as listed in Table 1.[2]

Table 1. Regulatory History of Bortezomib in the Adult Population Following Initial FDA Approval

FDA Approval Date	Approval Type	Description
March 25, 2005	New Indication	Treatment of multiple myeloma patients who have received at least 1 prior therapy.
December 8, 2006	New Indication	Treatment of multiple myeloma patients who have received at least 1 prior therapy. Treatment of mantle cell lymphoma patients who have received at least 1 prior therapy.
June 20, 2008	New Indication	Treatment of patients with multiple myeloma. Treatment of mantle cell lymphoma patients who have received at least 1 prior therapy.
January 23, 2012	New Route of Administration	For intravenous or subcutaneous injection use only.
October 8, 2014	New Indication	Treatment of patients with multiple myeloma. Treatment of patients with mantle cell lymphoma.

On August 14, 2015, the FDA granted the bortezomib sponsor pediatric exclusivity after the sponsor satisfied all elements in the FDA's Pediatric Written Request, dated November 13, 2012, in accordance with the BPCA.[3-5] Consequently, on September 14, 2015, the bortezomib U.S. prescribing information underwent a pediatric labeling change to reflect new information generated from a single-arm, non-randomized cooperative group trial (NCT0087309).[6-8] The safety and effectiveness of bortezomib in pediatric patients was not established in the trial as no clinical benefit was demonstrated in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL).[3,8] No new safety concerns were observed when bortezomib was added to a chemotherapy backbone. The adverse event profile of bortezomib was consistent with the

known adverse event profile in adults.[8] This review was triggered by the pediatric labeling change.

1.2 RELEVANT LABELED SAFETY INFORMATION

The bortezomib label contains the following information under the Highlights of Prescribing Information:[8]

CONTRAINDICATIONS

- Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. (4)
- Contraindicated for intrathecal administration. (4)

WARNINGS AND PRECAUTIONS

- Peripheral Neuropathy: Manage with dose modification or discontinuation. (2.7) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.7, 5.1)
- Hypotension: Use caution when treating patients taking anti-hypertensives, with a history of syncope, or with dehydration. (5.2)
- Cardiac Toxicity: Worsening of and development of cardiac failure has occurred. Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Pulmonary Toxicity: Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms. (5.4)
- Posterior Reversible Encephalopathy Syndrome: Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected. (5.5)
- Gastrointestinal Toxicity: Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia or Neutropenia: Monitor complete blood counts regularly throughout treatment. (5.7)
- Tumor Lysis Syndrome: Closely monitor patients with high tumor burden (5.8)
- Hepatic Toxicity: Monitor hepatic enzymes during treatment.(5.9)
- Embryo-fetal Toxicity: VELCADE can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy. (5.10)

ADVERSE 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)

USE IN SPECIFIC POPULATIONS

- Patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication. (8.8)

Under section 6 ADVERSE REACTIONS, the *Clinical Trials Safety Experience* and *Postmarketing Experience* subsections include: febrile neutropenia, stomatitis, ischemic colitis, bacteremia, pneumonia, sepsis, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia, and deep venous thrombosis.[8]

Under section 8 USE IN SPECIFIC POPULATIONS, the *Pediatric Use* subsection includes the following information:[8]

- The effectiveness of VELCADE in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established.
- The activity and safety of VELCADE in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with early relapsed (within 36 months of diagnosis) lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), a in a single-arm multicenter, non-randomized cooperative group trial. An effective reinduction multiagent

chemotherapy regimen was administered in 3 blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; block 2 included cyclophosphamide, etoposide and methotrexate; block 3 included high dose cytosine arabinoside and asparaginase. VELCADE was administered at a dose of 1.3 mg/m^2 as a bolus intravenous injection on days 1, 4, 8, and 11 of block 1 and days 1, 4, and 8 of block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was 10 years (range 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/ Alaska Native, 1% were Pacific Islander.

- The activity was evaluated in a pre-specified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤ 21 years and relapsed < 36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without VELCADE. There was no evidence that the addition of VELCADE had any impact on the CR rate.
- No new safety concerns were observed when VELCADE was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without VELCADE.
- The body surface area (BSA)-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*

Date of Search	July 3, 2018
Time Period of Search	September 14, 2015† - July 2, 2018
Search Type	Product Manufacturing Reporting Summary Quick Query
Product Terms	Product active ingredient: bortezomib
MedDRA Search Terms (Version 21.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† Pediatric labeling date

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from September 14, 2015 to July 2, 2018 with bortezomib.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from September 14, 2015 – July 2, 2018 with Bortezomib			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	5066 (2029)	4646 (1616)	896 (249)
Pediatrics (0 - <17 years)	116 (77)	110 (71)	25 (14)

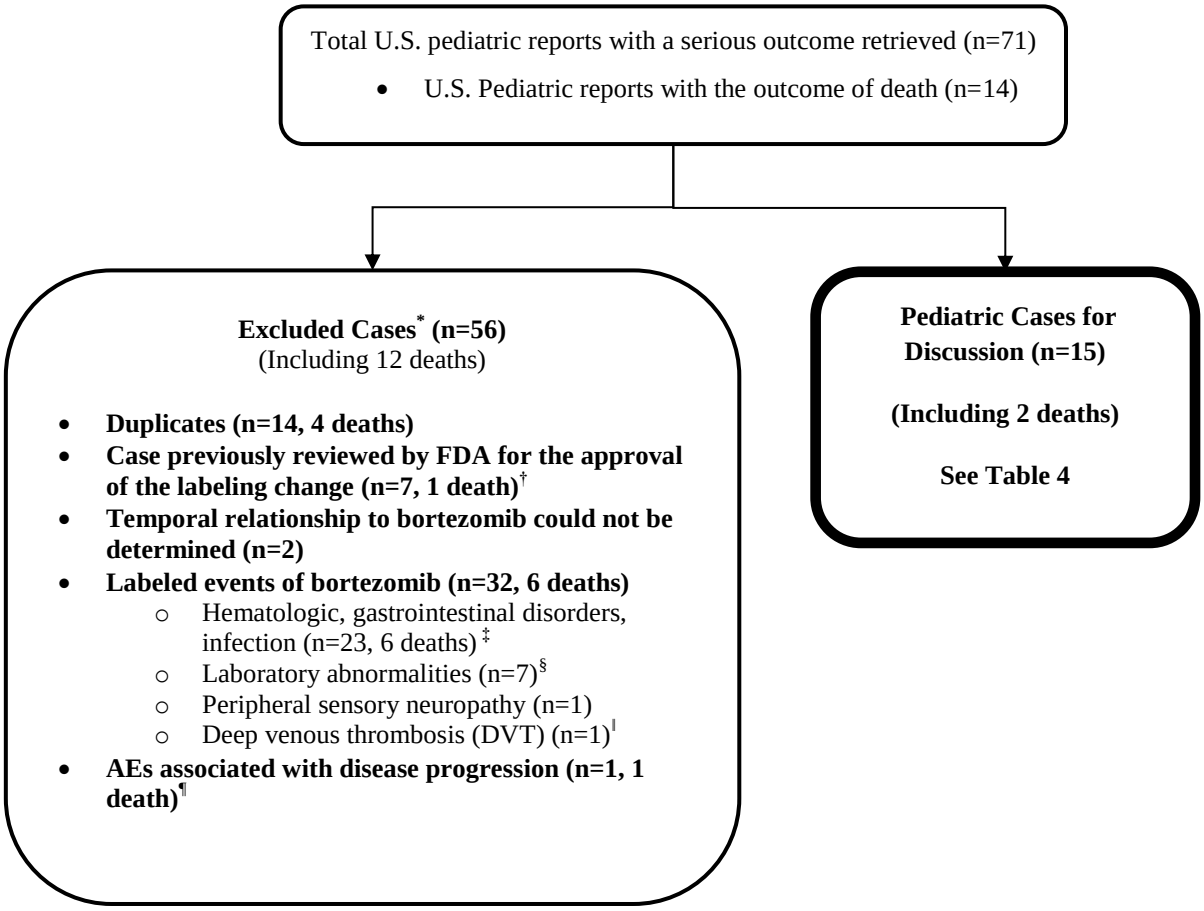
* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 71 U.S. serious pediatric reports (see Table 3). See **Figure 1.** below for the selection of cases to be summarized in **Sections 3.1.4 and 3.1.5.**

Figure 1. Selection of Serious U.S. Pediatric Cases with Bortezomib



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† Cases derived from study NCT01371981, which was previously reviewed in the approval for the labeling change.[3,9] Reported adverse events included colitis (n=2), multi-organ dysfunction (n=3, 1 death), sepsis (n=2) following concomitant administration of multiple chemotherapies.

‡ These cases contained a combination of hematologic adverse events (i.e. neutropenia, anemia, thrombocytopenia, febrile neutropenia, pancytopenia), gastrointestinal disorders (i.e. stomatitis, colitis), and/or infection (i.e. bacteremia, pneumonia, sepsis). All 23 cases reported contributory factors for these events, including underlying disease with bone marrow involvement and concomitant administration of multiple myelosuppressive chemotherapies. Among the six fatal reports, the cause of death was reported as sepsis or multi-organ failure related to infection (n=3), disease progression (n=2), and one case did not contain the patient's cause of death.

§ Laboratory abnormalities included elevated liver enzymes and bilirubin, hyperkalemia, hypokalemia, hyponatremia, hyperglycemia. All seven cases reported concomitant administration of pegaspargase, which is labeled for hepatotoxicity, and dexamethasone, which is labeled for hyperglycemia.[10,11]

‖ The case described a patient who developed a DVT at the same location where a peripherally inserted central catheter was present.

¶ One case with a fatal outcome described a patient who experienced complications of disease progression, including hypoxia and cardio-respiratory arrest, following concomitant administration of bortezomib and multiple chemotherapies; the reported cause of death was refractory ALL.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 15 pediatric cases.

Table 4 summarizes the characteristics of the 15 FAERS cases in U.S. pediatric patients with bortezomib reporting a serious outcome received by FDA from September 14, 2015 to July 2, 2018 included in the case series.

Table 4. Characteristics of the FAERS U.S. Serious Pediatric Cases with Bortezomib Received by FDA from September 14, 2015 to July 2, 2018 (N=15)

Age	2 - < 6 years	2
	6 - <12 years	3
	12 - < 17 years	10
Sex	Male	10
	Female	5
Reported Reason for Use	T-cell acute lymphoblastic leukemia (ALL)	12
	T-cell lymphoblastic lymphoma (LL)	2
	Autoimmune hemolytic anemia	1
Route of Administration	Intravenous	14
	Not reported	1
Serious Outcome*	Death	2
	Hospitalization	10
	Other serious	10
Reported Causes of Death (n=2)	Hyperammonemia	1
	Stroke	1

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.

3.1.4 Summary of Fatal Pediatric U.S. Cases (N=2)

We included two FAERS cases with bortezomib in the U.S. pediatric population reporting death as an outcome in our case series; both patients were enrolled in a clinical trial for T-cell ALL. One of the two cases reported a 14-year-old male who died from hyperammonemia associated with multiple areas of brain infarction and cerebral herniation within the first week of receiving asparaginase and bortezomib. Proton spectroscopy [magnetic resonance imaging (MRI)] also revealed elevated lactate and glutamate/glutamine. The other case reported a 13-year old male who died from a thrombotic stroke (MRI of the head confirmed multifocal infarct and previously noted sinusitis), with initial symptoms (such as severe headaches) occurring seven days after intrathecal methotrexate administration and 21 days after bortezomib 1.3 mg/m^2 and pegaspargase administrations. The reporter acknowledged the event was possibly related to sinusitis.

Reviewer's Comments: *The medical literature reports cases of hyperammonemia that occurred within five days of asparaginase administration, which fits with the time sequence described in the first case.*[12] *In this case of fatal hyperammonemia, the reporter also acknowledged that proton spectroscopy (MRI) findings "raised suspicion of a pre-existing urea cycle disorder." Regarding the second case, central nervous system thrombosis is labeled for both methotrexate and pegaspargase.*[10,13] *The medical literature describes cerebral thrombosis reported within 10 days following intrathecal methotrexate administration.*[14] *In both cases, there is reasonable temporality between bortezomib exposure and the fatal adverse event; however, it is impossible to attribute the fatal adverse event to a single medication or a pre-existing condition.*

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=13)

Among the 13 non-fatal cases in U.S. pediatric patients in our case series, no new safety signals were identified. A summary of these cases reporting serious, unlabeled events of interest, organized by System Organ Class (SOC), is provided below.

Blood and lymphatic system disorders (n=2)

- ***Hemolysis (n=1):*** A 10-year-old male was enrolled in a phase III trial evaluating the addition of bortezomib to a chemotherapy backbone in newly diagnosed T-cell ALL and T-cell LL patients. The patient received bortezomib (at unspecified dose) concomitantly with vincristine, dexamethasone, and daunorubicin as induction therapy, followed by methotrexate, vincristine, and mercaptopurine as interim maintenance therapy without bortezomib. Approximately 104 days after administration of the last bortezomib dose and two days following initiation of methotrexate and mercaptopurine, the patient experienced hemolysis with a hemoglobin drop from 9.5 to 6.9 (unit and reference range not reported) and a positive direct Coombs test. No further information was provided regarding action taken with these drugs. The patient subsequently received steroids, packed red blood cell transfusion, and intravenous immunoglobulin infusion for treatment of hemolysis. Hemolysis was not recovered at the time of the report.

  Reviewer's Comments: *Drug-induced immune hemolytic anemia usually occurs within a few days to two weeks following initiation of the drug.*[15] *Therefore, the event is unlikely related to bortezomib due to the long interval from bortezomib exposure to the onset of*

hemolysis. Mercaptopurine and methotrexate are reported in the literature as being associated with drug-induced immune hemolytic anemia.[16,17] *The short interval between methotrexate and mercaptopurine administration and the adverse event suggests hemolysis is likely attributable to these drugs. However, the lack of dechallenge and rechallenge information make it impossible to attribute the adverse event to a single medication.*

- ***Myelodysplastic syndrome (n=1):*** A 13-year-old female was enrolled in a phase III trial for treatment of newly diagnosed T-cell ALL and T-cell LL patients. The patient received bortezomib in combination with multiple chemotherapies during the induction and delayed intensification (including cyclophosphamide) phases of treatment for T-cell ALL. She subsequently received maintenance therapy without bortezomib. During cycle 9 of maintenance therapy with vincristine, dexamethasone, mercaptopurine, and methotrexate, the patient experienced persistent cytopenias, and a bone marrow biopsy was performed. On the same day as the biopsy, approximately 20 and 14 months following the first and last bortezomib doses, respectively, and an unspecified time after receiving cyclophosphamide, the patient was diagnosed with myelodysplastic syndrome (MDS) with a karyotype abnormality involving chromosome 7, and maintenance therapy was interrupted. Approximately one month following initial diagnosis of MDS, a follow-up bone marrow biopsy revealed the "bone marrow was hypoplastic but showed no dysplasia and no blasts," suggesting resolution of MDS. Therefore, MDS was reported as recovered. The patient subsequently resumed maintenance therapy with mercaptopurine and methotrexate at reduced doses.

  Reviewer's Comments*: Therapy-related MDS or AML involving chromosome 7 abnormalities is associated with alkylating agents, such as cyclophosphamide, and the latency period between the disease onset and treatment exposure can vary up to seven years.*[18,19] *Although MDS can progress into acute myeloid leukemia (AML), spontaneous remission without evolution of the disease is possible, as observed in this case.*[20,21] *DPV conducted a literature search that did not identify any articles implicating bortezomib's association with secondary and therapy-related MDS or AML. However, the administrations of bortezomib and cyclophosphamide prior to the MDS diagnosis make it impossible to attribute the adverse event to a single medication.*

Gastrointestinal disorders (n=3)

- ***Anal fissure (n=1), duodenal perforation (n=1), pneumoperitoneum (n=1):*** The reported age range for three cases was 13 through 16 years. All patients were enrolled in a phase III trial for treatment of newly diagnosed T-cell ALL and T-cell LL. Additionally, all cases reported onset of symptoms after receiving bortezomib concomitantly with dexamethasone and vincristine for 2-3 weeks. The case describing anal fissure reported constipation as a contributing cause. At the time of the report, the event outcome was unknown in one case (duodenal perforation) and recovering in two cases (anal fissure and pneumoperitoneum); the action taken with bortezomib was not reported in two cases and interrupted in one case.

Reviewer's Comments: *Bortezomib is labeled for constipation and small intestinal obstruction, which are plausible mechanisms for the development of anal fissures and pneumoperitoneum, respectively.*[8,22,23] *However, all patients received concomitant dexamethasone and vincristine, which are labeled for intestinal perforation.*[11,24] *Vincristine is also labeled for constipation, paralytic ileus, and intestinal necrosis.*[24] *The lack of dechallenge and rechallenge information make it impossible to attribute the adverse event to a single medication.*

Metabolism and nutrition disorders (n=4)

- ***Hypertriglyceridemia (n=2), hypophosphatemia (n=2):*** The reported age range for four cases was 5 through 15 years. All patients were enrolled in a phase III trial for treatment of newly diagnosed T-cell ALL and T-cell LL. In all four cases, the laboratory abnormalities were detected after receiving bortezomib in combination with pegaspargase and dexamethasone for 1-32 days. At the time of the report, the event outcome was recovering/recovered in all cases; the action taken with bortezomib was not reported in three cases, continued at the same dose in one case.

  Reviewer's Comments: *The medical literature describes cases of pegaspargase-induced hypertriglyceridemia and steroid-induced hypophosphatemia.*[25,26] *The lack of dechallenge and rechallenge information make it impossible to attribute the adverse event to a single medication.*

Miscellaneous (n=4)

- ***Focal dyscognitive seizures (n=1):*** One case of a 12-year-old female enrolled in a phase III trial for treatment of newly diagnosed T-cell ALL developed complex partial seizures nine and 27 days following the last doses of intrathecal methotrexate and bortezomib 1.3 mg/m^2, respectively. The patient was treated with lorazepam and levetiracetam. She was transferred to the epilepsy monitoring unit and continued to have symptoms at the time of the report. The action taken with bortezomib was reported as dose reduced.

  Reviewer's Comments: *Symptoms of seizures or cerebellar abnormalities typically occur within days or weeks of intrathecal chemotherapy administration; neurological events are well-documented toxicities with intrathecal injections, particularly in patients who receive multiple doses.*[27] *Neurotoxicity, including focal seizures, is labeled with methotrexate.*[13] *The reasonable temporality between focal dyscognitive seizures and intrathecal methotrexate suggests the event is more likely related to methotrexate.*[8]

- ***Infusion related reaction (n=1):*** One case of a 15-year-old male enrolled in a phase III trial for treatment of newly diagnosed T-cell LL received bortezomib on the same day as pegaspargase. The patient did not experience any immediate symptoms or reaction following bortezomib administration. During infusion of pegaspargase, the patient became pale, diaphoretic, and nauseated; vital signs included heart rate 134, respiratory rate 17, blood pressure 57/21, and oxygen saturation rate was 93% on room air. Pegaspargase infusion was stopped, and the patient's symptoms resolved after receiving normal saline bolus, diphenhydramine, and hydrocortisone. The action taken with bortezomib was reported as dose reduced. Approximately two months following the

initial infusion related reaction, the patient received another pegaspargase dose and experienced an anaphylactic reaction due to pegaspargase. Consequently, pegaspargase was discontinued.

Reviewer's Comments*: Symptoms of infusion-related reaction are similar to serious allergic reactions, and it can be difficult to differentiate the two conditions.*[28] *Both bortezomib and pegaspargase are labeled for serious allergic reactions and anaphylaxis.*[8,10] *However, the short interval between the adverse event and pegaspargase infusion, coupled with the development of anaphylactic reaction after repeat exposure to pegaspargase, suggest the adverse event is more likely related to pegaspargase.*

- ***Depressed level of consciousness (n=1):*** One case of a 15-year-old female enrolled in a phase III trial for treatment of newly diagnosed T-cell LL received bortezomib. The patient was also taking ziprasidone and lorazepam concomitantly for an unknown duration. Two days after bortezomib initiation, the patient experienced a transient episode of decreased level of consciousness upon awakening from sleep. She was minimally responsive to noxious stimuli and unable to speak with limited ability to move extremities. A computer tomography scan of the head and magnetic resonance imaging scan of the brain were negative. Her symptoms resolved without any treatment. The action taken with bortezomib was not reported.

  Reviewer's Comments: *Cognitive and motor impairment and excessive sedation are labeled for ziprasidone and lorazepam, respectively.*[29,30] *The lack of dechallenge and rechallenge information make it impossible to attribute the adverse event to a single medication.*

- ***Hypogammaglobulinemia (n=1):*** One case that was also reported in the literature described a 3-year-old female who initially received rituximab for steroid-dependent autoimmune hemolytic anemia.[31] A progressive decline in immunoglobulin level and absence of CD19 cells were noted two months after starting rituximab. Hypogammaglobulinemia persisted when bortezomib was administered concurrently with rituximab for an unknown duration. At the time of the report, the event outcome was not recovered; the action taken with bortezomib was not reported.

  Reviewer's Comments: *Hypogammaglobulinemia is labeled for rituximab.*[32] *The temporality of events with respect to rituximab suggests that hypogammaglobulinemia is more likely associated with rituximab. Hypogammaglobulinemia preceded bortezomib initiation; however, due to the lack of dechallenge and rechallenge information, it is impossible to determine whether bortezomib contributed to persistence of the adverse event.*

4 DISCUSSION

Of the 15 serious and unlabeled adverse event cases included in this series, no specific pattern or trend of unlabeled adverse events was noted. These cases described adverse events that can be

attributed to concomitant medications, or the cases had limited information, which precluded a meaningful causality assessment. Therefore, we identified no new safety signals, no increased severity of labeled adverse events, and no deaths that were solely attributed to bortezomib. The most commonly reported indications for bortezomib use were T-cell ALL and T-cell LL. These patients received bortezomib in addition to the standard treatment backbone, which comprises multiple cytotoxic chemotherapies (such as doxorubicin, cyclophosphamide, methotrexate, cytarabine) with IV fluids, asparaginase or pegaspargase, and high-dose steroids.[13,33-35]

5 CONCLUSION

DPV II did not identify any pediatric safety concerns for bortezomib at this time.

6 RECOMMENDATION

DPV II recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of bortezomib.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=15)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	12/18/2015	11853140	1	US-MALLINCKRODT-T201505658	Expedited (15-Day)	14	MALE	USA	DE,HO
2	12/21/2015	11855702	1	US-TAKEDA-2015MPI008545	Expedited (15-Day)	16	MALE	USA	HO
3	3/22/2016	12200866	2	US-TAKEDA-2016MPI001899	Expedited (15-Day)	6	MALE	USA	OT
4	4/28/2016	12314141	1	US-TAKEDA-2016MPI003082	Expedited (15-Day)	5	MALE	USA	OT
5	6/10/2016	12456075	1	US-TAKEDA-2016MPI002744	Expedited (15-Day)	15	FEMALE	USA	HO,OT
6	9/9/2016	12729876	1	US-TAKEDA-2016MPI007836	Expedited (15-Day)	13	MALE	USA	HO
7	9/21/2016	12767046	1	US-TAKEDA-2016MPI008022	Expedited (15-Day)	12	FEMALE	USA	HO
8	2/10/2017	13211375	2	US-TAKEDA-2017MPI000978	Expedited (15-Day)	13	MALE	USA	DE,HO,OT
9	4/18/2017	13452923	2	US-TAKEDA-2017MPI003035	Expedited (15-Day)	15	MALE	USA	HO,OT
10	8/9/2017	13849713	1	US-TAKEDA-2017MPI006531	Expedited (15-Day)	9	MALE	USA	HO,OT
11	10/25/2017	14125041	1	US-TAKEDA-2017MPI009322	Expedited (15-Day)	10	MALE	USA	HO,OT
12	10/26/2017	14127980	2	US-TAKEDA-2017MPI009253	Expedited (15-Day)	13	FEMALE	USA	OT
13	10/31/2017	14146938	1	US-TAKEDA-2017MPI009501	Expedited (15-Day)	15	MALE	USA	HO
14	11/17/2017	14198214	1	US-TAKEDA-2017MPI010008	Expedited (15-Day)	15	FEMALE	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
15	1/22/2018	14420863	1	US-ROCHE-1984120	Non-Expedited	3	FEMALE	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, OT=Other medically significant

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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