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Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sprycel (dasatinib) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dasatinib in pediatric patients.

Sprycel (dasatinib) is a kinase inhibitor and was initially approved in the U.S. on June 28, 2006. Dasatinib is currently indicated for:

- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
- Pediatric patients 1 year of age and older with Ph+ CML in chronic phase.
- Pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

This pediatric postmarketing safety review was prompted by pediatric labeling on December 18, 2018 that expanded the use of dasatinib to include use in pediatric patients 1 year of age and older with Ph+ CML in chronic phase and in pediatric patients 1 year and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

Five pediatric FAERS cases describe decreased methotrexate (MTX) clearance attributed to concurrent use of dasatinib and high-dose MTX. No objective measurement of MTX levels were reported but the maximum time to clear MTX to an undetectable level (<0.1 μM) ranged from 78 to 226 hours. Four of the cases required modification or discontinuation of the intended chemotherapy treatment plan and one received glucarpidase as an antidote to the elevated MTX level. Four of the five cases reported the following adverse events: acute kidney injury (n=2), pleural effusion (n=2), and mucositis (n=4).

DPV identified a potential new safety signal of a drug interaction between the concurrent administration of high-dose MTX and dasatinib from this pediatric postmarketing pharmacovigilance review. DPV will conduct further evaluation of this potential signal in accordance with the Center for Drug Evaluation and Research (CDER) Policy and Procedures for the collaborative identification, evaluation, and resolution of a newly identified safety signal (NISS). We opened a NISS (SS ID #1005375) on July 31, 2024, to further evaluate this potential risk. Additionally, DPV will continue routine pharmacovigilance monitoring with dasatinib.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sprycel (dasatinib) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dasatinib in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Sprycel (dasatinib) is a kinase inhibitor and was initially approved in the U.S. on June 28, 2006. Dasatinib is currently indicated for:

- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
- Pediatric patients 1 year of age and older with Ph+ CML in chronic phase.
- Pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

Phyrago (dasatinib) is a kinase inhibitor and was initially approved in the U.S. on December 5, 2023 and is currently indicated for the treatment of:[a,2]

- Newly diagnosed adults with Ph+ CML in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Ph+ ALL with resistance or intolerance to prior therapy.

This pediatric postmarketing safety review was prompted by pediatric labeling for Sprycel on December 18, 2018, that expanded the use of Sprycel to include use in pediatric patients 1 year of age and older with Ph+ CML in chronic phase and in pediatric patients 1 year and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

A pediatric safety review for dasatinib has not previously been presented to the Pediatric Advisory Committee.

[a] Pediatric use information is approved for Bristol-Myers Squibb Company's Sprycel (dasatinib) tablets. However, due to Bristol-Myers Squibb Company's marketing exclusivity rights, Phyrago (dasatinib) tablet is not labeled with that pediatric information.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Sprycel labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Sprycel labeling information, please refer to the full prescribing information.

----------CONTRAINDICATIONS----------

- None.

----------WARNINGS AND PRECAUTIONS----------

- *Myelosuppression and Bleeding Events:* Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated.
- *Fluid Retention:* Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification.
- *Cardiovascular Toxicity:* Monitor patients for signs or symptoms and treat appropriately.
- *Pulmonary Arterial Hypertension (PAH):* SPRYCEL may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed.
- *QT Prolongation:* Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval.
- *Severe Dermatologic Reactions:* Individual cases of severe mucocutaneous dermatologic reactions have been reported.
- *Tumor Lysis Syndrome:* Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL.
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise patients of reproductive potential of potential risk to fetus and to use effective contraception.
- *Effects on Growth and Development in Pediatric Patients:* epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients.
- *Hepatotoxicity:* Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction.

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥15%) in patients receiving SPRYCEL as single-agent therapy included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain.
- Most common adverse reactions (≥30%) in pediatric patients receiving SPRYCEL in combination with chemotherapy included mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, constipation, arrhythmia, hypertension, edema, infections (bacterial, viral and fungal), hypotension, decreased appetite, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, and altered state of consciousness.

----------DRUG INTERACTIONS----------

- *Strong CYP3A4 Inhibitors:* Dose reduction may be necessary.
- *Strong CYP3A4 Inducers:* Dose increase may be necessary.
- *Antacids:* Avoid simultaneous administration.
- *H2 Antagonists and Proton Pump Inhibitors:* Avoid coadministration.

----------USE IN SPECIFIC POPULATIONS----------

8.4 Pediatric Use

Ph+ CML in Chronic Phase

The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML [see Clinical Studies (14.3)]. There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients.

Ph+ ALL

The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported.

The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects.

Monitor bone growth and development in pediatric patients.

Pediatric Patients with Difficulty Swallowing Tablets

Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. The exposure for dispersed tablets was 36% lower as compared to intact tablets in pediatric patients [see Clinical Pharmacology (12.3)]. Due to the limited available clinical data, it is unclear whether dispersing SPRYCEL tablets significantly alters the safety and/or efficacy of SPRYCEL.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy[*]	
Date of search	May 23, 2024
Time period of search	June 28, 2006[†] - May 22, 2024
Search type	RxLogix Pediatric Focused Review Alert - DPV
Product terms	Product Active Ingredient: Dasatinib Product Name: Sprycel Active Moiety: Dasatinib Anhydrous
MedDRA search terms (Version 27.0)	All Preferred Terms

Table 1. FAERS Search Strategy*	
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Sprycel (dasatinib)
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

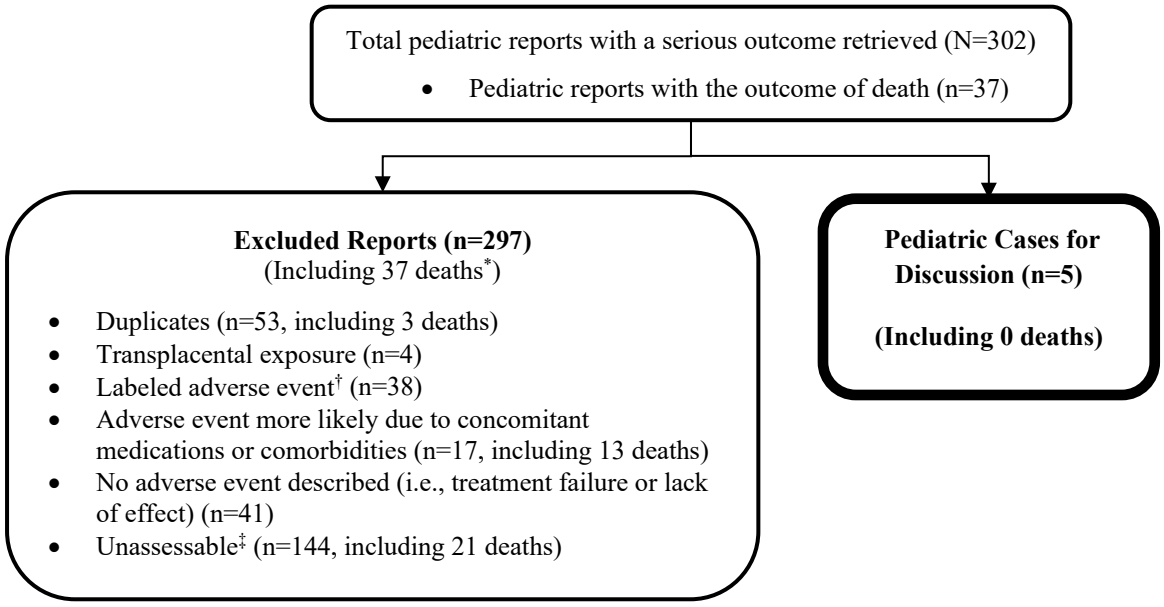
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 302 U.S. serious pediatric reports for patients less than 18 years old from June 28, 2006 through May 22, 2024.[b] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 297 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series. Appendix B contains a line listing of the 5 pediatric cases in the case series.

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



*Of the excluded U.S. FAERS reports, 37 described fatal outcomes. After accounting for duplicate reports (n=3), we identified 34 unique cases with a fatal outcome. None of the deaths were determined to be attributed to dasatinib. Thirteen cases described death resulting from progression of primary neoplastic disease. The remaining cases (n=21) had insufficient information to determine whether dasatinib contributed to fatal events.
† Labeled adverse event does not represent increased severity.
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

[b] Includes 5 pediatric reports that were identified among reports not coded with an age.

3.1.1 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.2 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=5)

We identified five U.S. pediatric FAERS cases with dasatinib reporting a non-fatal serious outcome received by FDA from June 28, 2006, through May 22, 2024. The following is a summary of each of the five FAERS cases. All five cases derive from a literature article[3] that described the results of a retrospective study of 121 patients with ALL aged 0.3-32.3 years receiving 1-5 g/m^2 MTX via a 24-hour infusion. The study aimed to determine if patients receiving dasatinib or imatinib concurrently with high-dose methotrexate (HDMTX) experienced slower MTX clearance than those not receiving a tyrosine kinase inhibitor concurrently with the HDMTX infusion. Dose reductions or omissions due to toxicity were made for subsequent HDMTX courses per protocol criteria or physician discretion. The five cases describe a potential drug interaction between the concurrent administration of HDMTX and dasatinib.

FAERS Case #15955390:
A 15-year-old male, with a body surface area=1.79 m^2, received HDMTX 5 g/m^2 infused over 24 hours and dasatinib 60 mg/m^2 (max 100 mg) 4 hours prior to the start of the methotrexate (MTX) infusion. The patient experienced acute kidney injury (46% increase in serum creatinine), delayed MTX clearance, and pleural effusion. The patient received 3000 units of glucarpidase and required 205 hours to reach an undetectable MTX level (<0.1 μM). Four courses of treatment with HDMTX were planned, the patient received one course, with subsequent courses omitted. No additional medical history or concomitant medications were reported. No additional clinical details were provided.

FAERS Case #16252303:
A 3-year-old male, with a BSA=0.66 m^2, received HDMTX 5 g/m^2 infused over 24 hours in the first and second course of receiving dasatinib 60 mg/m^2 (max 100 mg). The literature article reported that two courses of treatment with HDMTX were planned. For the first course, dasatinib was infused concurrently with HDMTX. For the second course, dasatinib was administered 4 hours after the start of HDMTX. The patient exhibited delayed MTX clearance: time for MTX level to be undetectable (<0.1 μM) was 103 hours for the first course and 60 hours for the second course. No toxicity was reported. The decreased MTX clearance was attributed to an interaction between dasatinib and MTX. Treatment with HDMTX was discontinued.

FAERS Case #16252378:
A 6-year-old female, with a BSA=0.79 m^2, received HDMTX 5 g/m^2 infused over 24 hours, concurrently with dasatinib 60 mg/m^2 (max 100 mg). The literature article reported that one course of treatment with HDMTX was planned. Following the first course, she exhibited delayed MTX clearance and mucositis. The time to onset of mucositis was not reported. The delayed MTX clearance and subsequent mucositis was attributed to an interaction between dasatinib and MTX. The MTX level decreased to an undetectable level (<0.1 μM) in 78 hours. Treatment with HDMTX was discontinued after one course.

FAERS Case #16252379:
A 6-year-old male, with a BSA=0.96 m^2, received HDMTX 5 g/m^2 infused over 24 hours. The literature article reported that eight courses of treatment with HDMTX were planned. For courses 1, 2, and 3; 3 g/m^2 infused over 24 hours for courses 4 and 5; and 4 g/m^2 infused over 24 hours for courses 6 and 7. Concurrently, he received dasatinib 60 mg/m^2 (max 100 mg) once a day at variable times relative to the initiation of the MTX infusion. Following treatment, he exhibited delayed MTX clearance and mucositis. The time to onset of mucositis was not reported but was reported to occur during courses 1, 2, and 3. MTX levels decreased to an undetectable level (<0.1 μM) in 121 hours following course 1, 84 hours following course 2, 252 hours following course 3, 60 hours following course 4, 62 hours following course 5, 60 hours following course 6, and 60 hours following course 7. The delayed MTX clearance and subsequent mucositis was attributed to an interaction between dasatinib and MTX, and the final remaining treatment course planned was discontinued.

FAERS Case #17829403:
A 6-year-old male, with a BSA=0.93 m^2, received HDMTX 5 g/m^2 infused over 24 hours and dasatinib 60 mg/m^2 (max 100 mg) was initiated 90 minutes after the initiation of the MTX infusion. The literature article reported that two courses of treatment with HDMTX were planned. Following the first course, the patient experienced acute kidney injury (294% increase in serum creatinine), mucositis, pleural effusion, and delayed MTX clearance. The time to onset of the reported toxicities was not provided. The MTX level decreased to an undetectable level (<0.1 μM) in 226 hours. Treatment with HDMTX was discontinued after one course.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with dasatinib in pediatric patients less than 18 years of age from June 28, 2006 through May 22, 2024. Of the 302 reports reviewed, 5 cases are included in our case series. These five pediatric FAERS cases describe decreased MTX clearance observed with concurrent use of dasatinib and HDMTX. The terminal half-life of MTX is 8 to 15 hours with 80-90% being excreted unchanged in the urine within 24 hours.[4] There are multiple factors that result in a high degree of patient variability in MTX clearance. Normal MTX elimination is defined by serum MTX levels below protocol-specified time points (e.g., ≤0.1 μM at 72 hours).[5] Ramsey et al. did not report serum MTX levels but the maximum time to clear MTX (<0.1 μM) ranged from 78 to 226 hours. Each of the five cases required modification or discontinuation of the intended chemotherapy treatment plan and one received glucarpidase as an antidote to the elevated MTX level. Four of the five cases reported the following adverse events: acute kidney injury (n=2), pleural effusion (n=1), and mucositis (n=3).

Acute kidney injury and mucositis are labeled in the WARNINGS AND PRECAUTIONS and OVERDOSAGE sections of the MTX labeling, respectively. Additionally, MTX is a hydrophilic drug and exits slowly from third space accumulations, such as pleural effusions, decreasing the clearance of MTX.[4] Dasatinib fluid retention, to include pleural effusions, is labeled in the WARNINGS AND PRECAUTIONS section of the product labeling.[1] A delayed clearance of MTX used in combination with dasatinib could be a concern due to the known adverse reaction of fluid retention with dasatinib use.

Decreased clearance of MTX is a significant concern when administering high-dose regimens and in patients with predisposing factors, such as, a baseline decreased kidney function or concomitant use of drugs that are known to increase MTX plasma concentrations. None of the five cases provide sufficient clinical details on the patient's medical history or concomitant drug use. However, this case series suggests a possible drug interaction with the concurrent administration of HDMTX and dasatinib, resulting in decreased MTX clearance. The potential risk is supported by a temporal relationship and biologic plausibility.

5 CONCLUSION

DPV identified a potential new safety signal of a drug interaction between the concurrent administration of HDMTX and dasatinib from this pediatric postmarketing pharmacovigilance review. DPV will conduct further evaluation of this potential signal in accordance with the Center for Drug Evaluation and Research (CDER) Policy and Procedures for the collaborative identification, evaluation, and resolution of a newly identified safety signal (NISS).[6] We opened a NISS (SS ID #1005375) on July 31, 2024, to further evaluate this potential risk. Additionally, DPV will continue routine pharmacovigilance monitoring with dasatinib.

6 REFERENCES

1. Sprycel (dasatinib) [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. Revised July 2024.

2. Phyrago (dasatinib) [package insert]. New Brighton, MN. Nanocopoeia, LLC. Revised December 2024.

3. Ramsey LB, Mizuno T, Vinks AA, O'Brien MM. Delayed methotrexate clearance in patients with acute lymphoblastic leukemia concurrently receiving dasatinib. Pediatr Blood Cancer. 2019;66: e27618. https://doi.org/10.1002/pbc.27618.

4. Methotrexate Sodium, Injection. Lake Forest, IL. Hospira, Inc. Revised November 2023.

5. Hamed KM, Dighriri IM, Baomar AF, et al. Overview of Methotrexate Toxicity: A Comprehensive Literature Review. Cureus. 2022;14: e29518.

6. FDA Manual of Policies and Procedures. Office of the Center Director. Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS). April 2020. Accessed on January 20, 2025 at: https://www.fda.gov/media/137475/download?attachment

7 APPENDICES

7.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=5)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	13-FEB-2019	15955390	1	US-ACCORD-105914	Expedited (15-Day)	15	Male	USA	Hospitalization, Other
2	29-APR-2019	16252303	5	US-MYLANLABS-2019M1039697	Expedited (15-Day)	3	Male	USA	Other
3	29-APR-2019	16252379	2	US-MYLANLABS-2019M1039761	Expedited (15-Day)	6	Male	USA	Other
4	29-APR-2019	16252378	2	US-MYLANLABS-2019M1039732	Expedited (15-Day)	6	Female	USA	Other
5	27-MAY-2020	17829403	2	US-PFIZER INC-2020203227	Expedited (15-Day)	6	Male	USA	Other

*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, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report. Therefore, a serious outcome may not apply to all adverse events in a FAERS report. A review of the FAERS report narrative is necessary to determine adverse event-level outcomes and any association to a suspect product.

Abbreviations: DE=death, HO=hospitalization, LT=life-threatening, DS=disability, CA=congenital anomaly, OT=other medically significant, RI=required intervention