Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: May 30, 2023

Safety Evaluator: Omayma Kishk, PharmD, BCPPS
Division of Pharmacovigilance-I (DPV-I)

Medical Officer: Ivone Kim, MD
DPV-I

Team Leader: Carmen Cheng, PharmD
DPV-I

Division Director (Acting): Monica Muñoz, PharmD, PhD, BCPS
DPV-I

TTT Record ID: 2023-3925

Product Name	Pediatric Labeling Approval Date	Application Type/Number	Applicant
Jevtana Kit (cabazitaxel) solution; intravenous	May 17, 2017	NDA 201023	Sanofi Aventis US
Cabazitaxel solution; intravenous	Not applicable	ANDA 207693	Accord Healthcare, Inc.
Cabazitaxel solution; intravenous	Not applicable	ANDA 207718	Dr. Reddy's
Cabazitaxel solution; intravenous	Not applicable	ANDA 207736	Apotex
Cabazitaxel solution; intravenous	Not applicable	NDA 207949	Accord Healthcare, Inc.
Cabazitaxel solution; intravenous	Not applicable	NDA 208715	Sandoz Inc.

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) for cabazitaxel in pediatric patients through age 17 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 U.S. serious unlabeled adverse events associated with cabazitaxel in pediatric patients.

Jevtana (cabazitaxel) is a microtubule inhibitor administered intravenously initially approved by the FDA on June 17, 2010. Cabazitaxel is currently indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change on May 17, 2017. The labeling was updated to include findings that cabazitaxel failed to show efficacy in pediatric patients with recurrent or refractory high grade glioma or diffuse pontine glioma.

DPV reviewed all U.S. serious FAERS reports for cabazitaxel in the pediatric population (ages 0 to <18 years) from June 17, 2010, through March 21, 2023. Our evaluation did not identify any cases reporting unlabeled adverse event associated with cabazitaxel in the pediatric population. DPV detected no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to cabazitaxel.

DPV will continue to monitor all adverse events associated with the use of cabazitaxel.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) for cabazitaxel in pediatric patients through age 17 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 U.S. serious unlabeled adverse events associated with cabazitaxel in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Cabazitaxel is a microtubule inhibitor administered intravenously initially approved by the FDA on June 17, 2010. Cabazitaxel is currently indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment.[1]

On May 17, 2017, the labeling for cabazitaxel was updated to include findings from results of clinical trial TED12689 (NCT01751308), an open label, multi-center study conducted in two parts. Phase 1 of the study used dose escalation to establish the maximum tolerated dose of cabazitaxel in pediatric patients with recurrent or refractory solid tumors based on related dose limiting toxicities. Phase 2 evaluated the activity and safety of cabazitaxel at the maximum tolerated dose in pediatric patients with recurrent or refractory high grade glioma or diffuse intrinsic pontine glioma. Study findings and FDA clinical review determination are reproduced below from the cabazitaxel pediatric clinical review.[2]

"The adverse event profile of cabazitaxel in the pediatric population studied appears to be similar to that of the adult population. However, the pediatric studies failed to demonstrate that cabazitaxel is effective in the treatment of pediatric patients with recurrent or refractory high grade glioma or diffuse pontine glioma. Therefore, use of cabazitaxel in this population is not recommended."

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change on May 17, 2017. DPV has not previously presented cabazitaxel to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The cabazitaxel labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[1] For further labeling information, please refer to the full prescribing information.

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

See full prescribing information for complete boxed warning.

- **Neutropenic deaths have been reported. Obtain frequent blood counts to monitor for neutropenia. JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm^3. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m^2 (4, 5.1, 5.2)**
- **Severe hypersensitivity can occur and may include generalized rash/erythema, hypotension and bronchospasm. Discontinue JEVTANA immediately if severe reactions occur and administer appropriate therapy. (2.1, 5 2)**
- **Contraindicated if history of severe hypersensitivity reactions to cabazitaxel or to drugs formulated with polysorbate 80. (4)**

----------**CONTRAINDICATIONS**----------

- Neutrophil counts of ≤1,500/mm^3 (2.2, 4)
- History of severe hypersensitivity to JEVTANA or polysorbate 80 (4)
- Severe hepatic impairment (Total Bilirubin >3 × ULN) (4)

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

- Bone marrow suppression (particularly neutropenia) and its clinical consequences (febrile neutropenia, neutropenic infections, and death): Monitor blood counts frequently to determine if dosage modification or initiation of G-CSF is needed. Closely monitor patients with hemoglobin <10 g/dL. (2.2, 4, 5.1)
- Increased toxicities in elderly patients: Patients ≥65 years of age were more likely to experience fatal outcomes and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely. (5.2, 8.5)
- Hypersensitivity: Severe hypersensitivity reactions can occur. Premedicate with corticosteroids and H_2 antagonists. Discontinue infusion immediately if hypersensitivity is observed and treat as indicated. (4, 5.3)
- Gastrointestinal disorders: Nausea, vomiting, and diarrhea may occur. Mortality related to diarrhea has been reported. Rehydrate and treat with antiemetics and antidiarrheals as needed. If experiencing Grade ≥3 diarrhea, dosage should be modified. (2.2) Deaths have occurred due to gastrointestinal hemorrhage, perforation and neutropenic enterocolitis. Delay or discontinue JEVTANA and treat as indicated. (5.4)
- Renal failure, including cases with fatal outcomes, has been reported. Identify cause and manage aggressively. (5.5)
- Urinary disorders including cystitis: Cystitis, radiation cystitis, and hematuria may occur. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis. Interrupt or discontinue JEVTANA and provide medical or surgical supportive care, as needed, in patients experiencing severe hemorrhagic cystitis.
- Respiratory disorders: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome, including fatal outcomes, have been reported. Delay or discontinue JEVTANA and treat as indicated. (5.7)

- Hepatic impairment: Administer JEVTANA at a dose of 20 mg/m^2 in patients with mild hepatic impairment. Administer JEVTANA at a dose of 15 mg/m^2 in patients with moderate hepatic impairment. (2.3, 5.8)
- Embryo-fetal toxicity: JEVTANA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception. (5.9, 8.1, 8.3)

----------**ADVERSE REACTIONS**----------

Most common all grades adverse reactions and laboratory abnormalities (≥10%) with JEVTANA 20 mg/m^2 or 25 mg/m^2 are neutropenia, anemia, diarrhea, nausea, fatigue, asthenia, vomiting, hematuria, constipation, decreased appetite, back pain, and abdominal pain. (6)

8.4 Pediatric Use

The safety and effectiveness of JEVTANA in pediatric patients have not been established.

JEVTANA was evaluated in 39 pediatric patients (ages 3 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m^2 intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid premedication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearances by body surface area were comparable to those in adults.

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	March 22, 2023
Time period of search	June 17, 2010[†] - March 21, 22023
Search type	RxLogix PV Signal Quick Query
Product terms	Product Active Ingredient: Cabazitaxel, cabazitaxel acetone
MedDRA search terms (Version 25.1)	All PT terms
* See Appendix A for a description of the FAERS database. [†] U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

Table 2 presents the number of adult and pediatric FAERS reports from June 17, 2010, through March 21, 2023 with cabazitaxel.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From June 17, 2010, through March 21, 2023 With Cabazitaxel

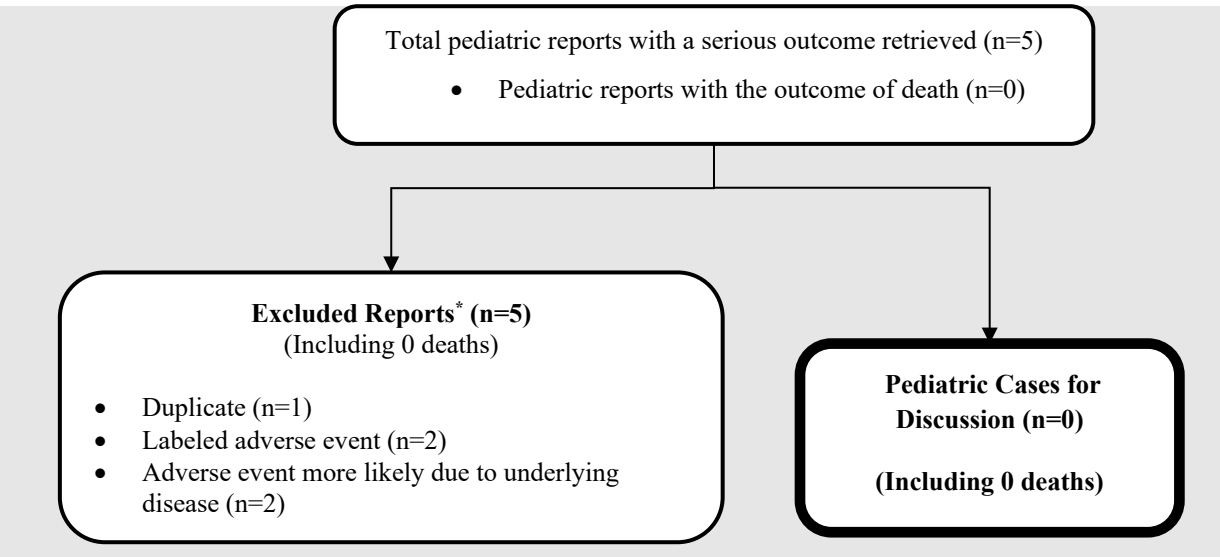
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	1,787 (495)	382 (5)	491 (95)
Pediatrics (0 - <18 years)	6 (5)	6‡ (5)	0‡ (0)

* 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, or other serious important medical events.
‡ See Figure 1.

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

Our FAERS search retrieved 5 U.S. serious pediatric reports from June 17, 2010, through March 21, 2023. We excluded all 5 reports from the case series for the following reasons: duplicate report (n=1), labeled adverse event (n=2), and adverse event more likely due to underlying disease (n=2). **Figure 1** presents the selection of cases for the pediatric case series.

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



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

3.1.2 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion

3.1.3 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with cabazitaxel in the pediatric population.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports for cabazitaxel in the pediatric population (ages 0 to <18 years) from June 17, 2010, through March 21, 2023. Our evaluation did not identify any cases reporting unlabeled adverse event associated with cabazitaxel in the pediatric population. There were no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to cabazitaxel.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for cabazitaxel at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of cabazitaxel.

7 REFERENCES

1. Jevtana (cabazitaxel) injection, for intravenous use [Prescribing Information]. Bridgewater, NJ: sanofi-aventis U.S. LLC; February 2021.
2. Barone A, Demko S. Medical Officer Review of Jevtana (cabazitaxel) for injection. April 2017. https://www.fda.gov/media/105645/download.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 (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.

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