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Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	March 11, 2025
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Product Name:	Abraxane (paclitaxel protein-bound particles for injectable suspension)
Pediatric Labeling Approval Date:	December 6, 2019
Application Type/Number:	NDA 021660
Applicant:	Bristol-Myers Squibb
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Abraxane (paclitaxel protein-bound particles for injectable suspension) in pediatric patients less than 17 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 paclitaxel in pediatric patients.

Abraxane (paclitaxel protein-bound particles for injectable suspension) is a microtubule inhibitor approved in the U.S. on January 7, 2005. Abraxane is currently indicated for:

- Metastatic breast cancer: treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Non-small cell lung cancer: first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Adenocarcinoma of the pancreas: first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Paclitaxel is not indicated for use in pediatric patients.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on December 6, 2019, which included information on clinical studies that failed to establish safety and effectiveness for paclitaxel in pediatric patients.

DPV reviewed all U.S. serious FAERS reports with paclitaxel in pediatric patients less than 17 years of age from January 7, 2005 - January 20, 2025, and identified 120 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with paclitaxel in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for paclitaxel at this time and will continue routine pharmacovigilance monitoring for paclitaxel.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Abraxane (paclitaxel protein-bound particles for injectable suspension) in pediatric patients less than 17 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 paclitaxel in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Abraxane (paclitaxel protein-bound particles for injectable suspension) is a microtubule inhibitor approved in the U.S. on January 7, 2005. Abraxane is currently indicated for:

- Metastatic breast cancer: treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Non-small cell lung cancer: first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Adenocarcinoma of the pancreas: first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Paclitaxel is also available as a nonaqueous solution for injection. However, paclitaxel solution for injection and paclitaxel protein-bound particles for injectable suspension cannot be substituted. The dosing, administration, indications, and safety considerations between the two products differ.[2] The Abraxane labeling states: Do not substitute Abraxane for other paclitaxel products.

Abraxane (paclitaxel protein-bound particles for injectable suspension) and paclitaxel injection, solution are not indicated for use in pediatric patients.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on December 6, 2019, which included information on clinical studies that failed to establish safety and effectiveness for paclitaxel in pediatric patients.

Paclitaxel has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

WARNING: SEVERE MYELOSUPPRESSION

See full prescribing information for complete boxed warning.

- **Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm^3.**
- **Monitor for neutropenia, which may be severe and result ininfection or sepsis.**
- **Perform frequent complete blood cell counts on all patients receiving ABRAXANE.**

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

- Neutrophil counts of < 1,500 cells/mm^3.
- Severe hypersensitivity reactions to ABRAXANE.

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

- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption.
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels.
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine.
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not rechallenge with this drug.
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, consider dose reduction and closely monitor patients with hepatic impairment.
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission.
- ABRAXANE can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

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

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea.
- The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration.

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pharmacokinetics, safety, and antitumor activity of ABRAXANE were assessed in an open-label, dose escalation, dose expansion study (NCT01962103) in 96 pediatric patients aged 1.4 to < 17 years with recurrent or refractory pediatric solid tumors. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. No new safety signals were observed in pediatric patients across these studies.

Paclitaxel protein-bound exposures normalized by dose were higher in 96 pediatric patients (aged 1.4 to < 17 years) as compared 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	January 21, 2025
Time period of search	January 7, 2005† - January 20, 2025
Search type	RxLogix Pediatric Focused Review Alert
Product terms	Product Active Ingredient: Paclitaxel
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Abraxane (paclitaxel)
‡ 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.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

3 RESULTS

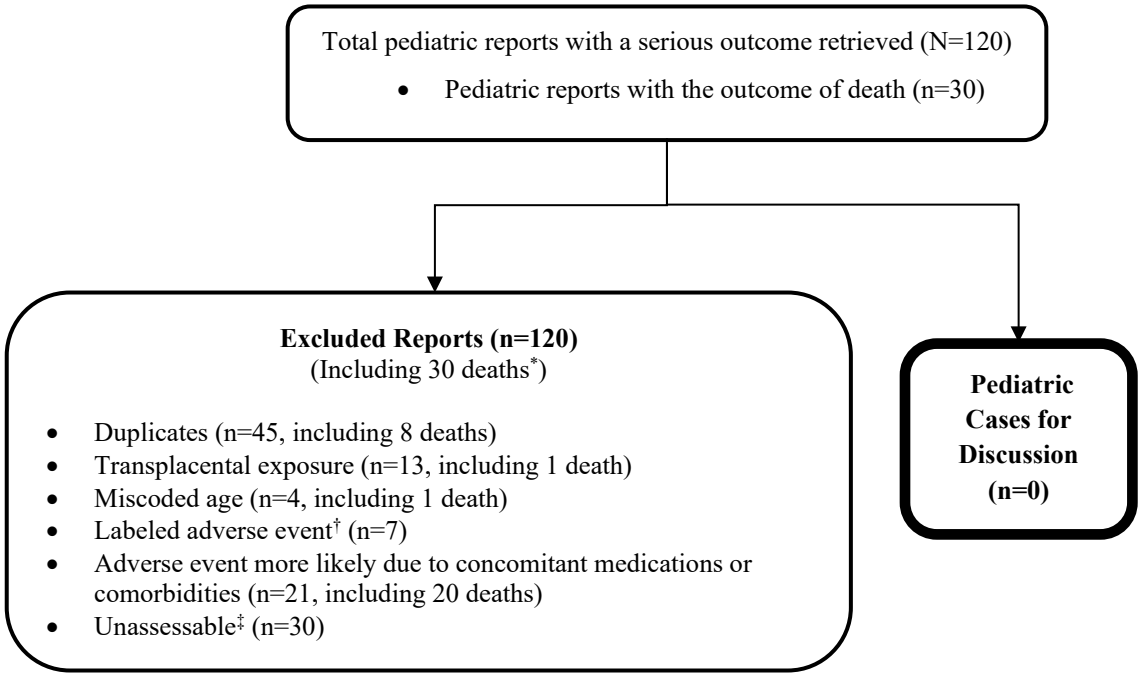
3.1 FAERS

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

Our FAERS search retrieved 120 U.S. serious pediatric reports for patients less than 17 years old from January 7, 2005, through January 20, 2025.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 120 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

[a] Includes four pediatric reports that were identified among reports not coded with an age.

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



* Of the excluded U.S. FAERS reports, 30 described fatal outcomes. After accounting for duplicate reports (n=8), we identified 22 unique cases describing fatal outcomes. None of the deaths were determined to be attributed to paclitaxel. One death case described an adult patient. One death case described fetal death after in utero exposure to multiple chemotherapeutic agents. Twenty cases described death resulting from progression of primary neoplastic disease.

† 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.

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

There are no fatal pediatric adverse event cases for discussion.

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

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with paclitaxel in pediatric patients less than 17 years of age from January 7, 2005† - January 20, 2025, and identified 120 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with paclitaxel in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for paclitaxel at this time and will continue routine pharmacovigilance monitoring for paclitaxel.

6 REFERENCES

1. Abraxane (paclitaxel) [package insert]. Summit, NJ. Celgene Corporation. Revised August 2020.

2. Paclitaxel Product Label. Revised September 2024. Available at: https://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/a1eb16b4-285b-4e81-9c4e-1244d4a52af8/spl-doc . Accessed: February 14, 2025.

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.