**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

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|---|---|
| **Date:** | September 18, 2023 |
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| **Product Name:** | Yondelis (trabectedin) |
| **Pediatric Labeling Approval Date:** | June 29, 2018 |
| **Application Type/Number:** | NDA 207953 |
| **Applicant:** | Janssen Products, LP |
| **TTT Record ID:** | 2023-5500 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Yondelis (trabectedin) 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 serious unlabeled adverse events associated with trabectedin in pediatric patients.

Trabectedin is an alkylating drug, initially approved in the U.S. on October 23, 2015. Trabectedin is currently indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. This pediatric postmarketing safety review was stimulated by the Yondelis pediatric labeling on June 29, 2018, that included clinical data regarding studies in pediatric patients. Safety and effectiveness in pediatric patients have not been established for trabectedin. Trabectedin has not been previously presented to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with trabectedin in pediatric patients less than 17 years of age received by FDA through July 10, 2023. All of the 23 reports reviewed were excluded from further discussion after hands-on evaluation.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with trabectedin in pediatric patients less than 17 years of age. DPV will continue routine pharmacovigilance monitoring for trabectedin.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Yondelis (trabectedin) 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 serious unlabeled adverse events associated with trabectedin in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY[1]

Trabectedin is an alkylating drug, initially approved in the U.S. on October 23, 2015. Trabectedin is currently indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. This pediatric postmarketing safety review was stimulated by the Yondelis pediatric labeling on June 29, 2018, that included clinical data regarding studies in pediatric patients. Safety and effectiveness in pediatric patients have not been established for trabectedin. Trabectedin has not been previously presented to the Pediatric Advisory Committee.

## 1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

----------CONTRAINDICATIONS----------
Known hypersensitivity to trabectedin (4)

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

- Neutropenic sepsis: Severe, and fatal, neutropenic sepsis may occur. Monitor neutrophil count during treatment. Withhold YONDELIS for Grade 2 or greater neutropenia (5.1)
- Rhabdomyolysis: Rhabdomyolysis may occur; withhold YONDELIS for severe or life-threatening increases in creatine phosphokinase level (5.2)
- Hepatotoxicity: Hepatotoxicity may occur. Monitor and delay and/or reduce dose if needed (5.3)
- Cardiomyopathy: Severe and fatal cardiomyopathy can occur. Withhold YONDELIS in patients with left ventricular dysfunction (5.4)
- Capillary leak syndrome: Monitor and discontinue YONDELIS for capillary leak syndrome (5.5)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use effective contraception (5.7, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most common (≥20%) adverse reactions are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia, increased ALT, thrombocytopenia, anemia, increased AST, and increased creatine phosphokinase. (6.1)

**8.4 Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

Safety (n=61) and efficacy (n=58) were assessed across five open-label studies (NCT00006463, NCT01453283, NCT00005625, NCT00070109, and ET-B-023-00) in pediatric patients (aged 2 to <17 years) with pediatric histotypes of sarcoma (predominantly rhabdomyosarcoma,

osteosarcoma, Ewing sarcoma, and non-rhabdomyosarcoma soft tissue sarcoma). No new safety signals were observed in pediatric patients across these studies.

Pharmacokinetic parameters in 17 pediatric patients (aged 3 to 17 years) were within the range of values previously observed in adults given the same dose per body surface area.

# 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 | July 11, 2023 |
| Time period of search | All reports through July 10, 2023 |
| Search type | RxLogix Post-Market Cases |
| Product terms | Product active ingredient: Trabectedin |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities | |

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 1 presents the number of adult and pediatric FAERS reports from all dates through July 10, 2023, with trabectedin.

**Table 1. Total Adult and Pediatric FAERS Reports* Received by FDA through July 10, 2023, With Trabectedin**

| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
|---|---|---|---|
| Adults (≥ 17 years) | 1341 (207) | 1294 (171) | 233 (47) |
| Pediatrics (0 - <17 years) | 23 (8) | 23 (8) | 6 (2) |

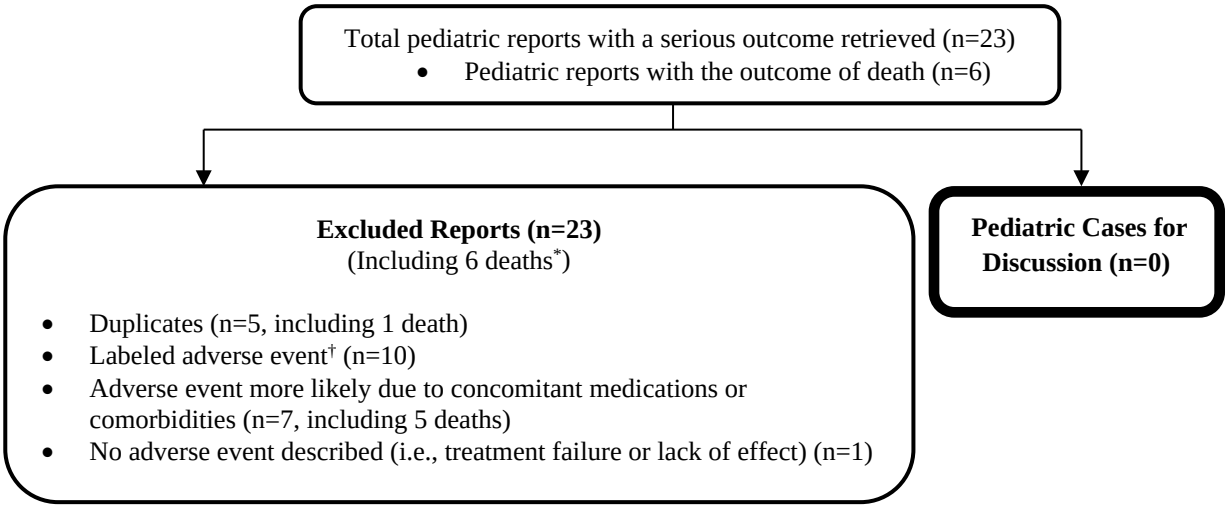
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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.

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

Our FAERS search retrieved 23 serious pediatric reports received by FDA through July 10, 2023. We reviewed all pediatric reports with a serious outcome. We excluded all reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

**Figure 1. Selection of Serious Pediatric Cases with Trabectedin**




* Six excluded FAERS reports described fatal outcomes, including one duplicate report. All deaths were attributable to progression of primary neoplastic disease.

† Labeled adverse event does not represent increased severity or frequency.

‡ 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.

#### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

#### *3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)*

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

## 4 DISCUSSION

DPV reviewed all serious FAERS reports with trabectedin in pediatric patients less than 17 years of age received by FDA through July 10, 2023 (n=23). All 23 reports reviewed were excluded from further discussion after hands-on evaluation.

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

## *5* CONCLUSION

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

# 6 REFERENCES

1. Yondelis (trabectedin) for injection, for intravenous use [package insert]. Horsham, PA; Janssen Products, LP. June, 2020.

# 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 (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 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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