**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:** | November 22, 2022 |
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| **Product Name:** | Granix (tbo-filgrastim) |
| **Pediatric Labeling Approval Date:** | July 31, 2018 |
| **Application Type/Number:** | BLA 125294 |
| **Applicant:** | Sicor Biotech UAB |
| **TTT Record ID#:** | 2022-2497 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Granix (tbo-filgrastim) in pediatric patients <17 years of age. 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) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with tbo-filgrastim in pediatric patients.

The FDA first approved Granix (tbo-filgrastim) on August 29, 2012, for the reduction in the duration of severe neutropenia in adult patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. This review was prompted by the pediatric labeling change on July 31, 2018, that expanded the indication to include pediatric patients 1 month and older.

DPV reviewed all U.S. serious FAERS reports with tbo-filgrastim in the pediatric population (ages 0 - <17 years) from August 29, 2012, through October 23, 2022, and did not identify any cases for inclusion in a case series.

DPV did not identify any new pediatric safety concerns for tbo-filgrastim at this time and will continue to monitor all adverse events associated with the use of tbo-filgrastim.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Granix (tbo-filgrastim) in pediatric patients <17 years of age. 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) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with tbo-filgrastim in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY[1]

Granix (tbo-filgrastim) is a leukocyte growth factor, first approved on August 29, 2012, for the reduction in the duration of severe neutropenia in adult patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

This review was prompted by the pediatric labeling change on July 31, 2018, that expanded the indication to include pediatric patients 1 month and older.

The safety and efficacy in pediatric patients were based on evidence from studies of tbo-filgrastim in adults with additional safety and pharmacokinetics data from a single-arm trial of 50 pediatric patients with solid tumors treated with tbo-filgrastim for chemotherapy-induced neutropenia. The 50 pediatric patients ranged in age from 1 month to < 17 years old. The pharmacokinetics and safety profile of tbo-filgrastim in the pediatric population were similar to those seen in adults. The most common (>5%) adverse reactions in pediatric patients included thrombocytopenia (34%), pyrexia (8%), pain in extremity (6%), headache (6%) and diarrhea (6%). There is no data for the age group < 1 month old.[2]

DPV has not previously presented an evaluation of postmarketing adverse event reports for tbo-filgrastim in pediatric patients to the Pediatric Advisory Committee (PAC).

## 1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Contraindications, Warnings and Precautions, Adverse Reactions (from the Highlights of Prescribing Information), and the Pediatric Use sections of the tbo-filgrastim product labeling are reproduced below.

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

- Patients with a history of serious allergic reactions to filgrastim products or pegfilgrastim products.

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

- Fatal Splenic Rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture
- Acute Respiratory Distress Syndrome (ARDS): Monitor for and manage immediately. Discontinue GRANIX if suspected
- Serious Allergic Reactions Including Anaphylaxis: Permanently discontinue GRANIX in patients with serious allergic reactions
- Sickle Cell Disorders: Severe and sometimes fatal crisis can occur Discontinue GRANIX if suspected
- Glomerulonephritis: Evaluate and consider dose reduction or interruption of GRANIX if causality is likely
- Capillary Leak Syndrome: Monitor if symptoms develop and administer standard symptomatic treatment

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

- Most common adverse reaction (≥1%) to GRANIX is bone pain

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

8.4 Pediatric Use

The safety and effectiveness of GRANIX have been established for pediatric patients 1 month to < 17 years old (no data for the age group < 1 month old). Use of GRANIX in these age groups is supported by evidence from adequate and well-controlled studies of GRANIX in adults with additional safety and pharmacokinetics data from a single-arm trial of 50 pediatric patients with solid tumors treated with GRANIX for chemotherapy-induced neutropenia. The 50 pediatric patients had a median age of 9.2 years (range, 1.4-15.9 years); 2 were infants (1 month to < 2 years old), 30 were children (2 to < 12 years old), and 18 were adolescents (12 to < 17 years old). The pharmacokinetics and safety profile of GRANIX in the pediatric population were similar to those seen 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 | October 24, 2022 |
| Time period of search | August 29, 2012† - October 23, 2022 |
| Search type | RxLogix PV Reports Quick Query |
| Product terms | Product Active Ingredient: tbo-filgrastim |

| Table 1. FAERS Search Strategy* | |
|---|---|
| MedDRA search terms (Version 25.0) | All PTs |

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Granix (tbo-filgrastim)
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

# 3 RESULTS

## 3.1 FAERS

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

Table 2 presents the number of adult and pediatric FAERS reports from August 29, 2012, through October 23, 2022, with tbo-filgrastim.

**Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 29, 2012 through October 23, 2022 with tbo-filgrastim**

| | All reports (U.S.) | Serious† (U.S.) | Death (U.S.) |
|---|---|---|---|
| Adults (≥ 17 years) | 127 (126) | 88 (87) | 24 (24) |
| Pediatrics (0 - <17 years) | 8 (4) | 6 **(2)** | 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.

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

Our FAERS search retrieved 2 U.S. serious pediatric reports for tbo-filgrastim from August 29, 2012, through October 23, 2022.

No cases were identified for inclusion in a pediatric case series. We reviewed the two U.S. FAERS pediatric reports with a serious outcome and determined the reports were unassessable because insufficient information was reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information was contradictory, or information provided in the case could not be supplemented or verified.

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

We did not identify any FAERS U.S. serious fatal pediatric adverse event cases associated with tbo-filgrastim in the pediatric population for discussion.

### *3.1.4 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 tbo-filgrastim in the pediatric population.

## 4 DISCUSSION

DPV reviewed two FAERS U.S. serious reports with tbo-filgrastim in the pediatric population (ages 0 - <17 years) from August 29, 2012, through October 23, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths associated with tbo-filgrastim.

## 5 CONCLUSION

DPV did not identify any new pediatric safety concerns for tbo-filgrastim at this time.

## 6 RECOMMENDATION

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

## 7 REFERENCES

1. Granix (tbo-filgrastim) [package insert]. Vilnius, Lithuania, Sicor Biotech UAB. Revised March 2019.

2. Granix (tbo-filgrastim) [package insert]. Vilnius, Lithuania, Sicor Biotech UAB. Revised July 2018.

# 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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