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:	June 30, 2025
Reviewers:	Debra Ryan, PharmD, MBA, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Enbrel (etanercept) injection
Pediatric Labeling Approval Date:	October 18, 2023
Application Type/Number:	BLA 103795
Applicant:	Immunex Corporation
TTT Record ID:	2025-14529

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Enbrel (etanercept) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with etanercept in pediatric patients.

Enbrel (etanercept) injection was initially approved in the U.S. on November 2, 1998. Etanercept is a tumor necrosis factor blocker indicated for the treatment of adult patients with rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; and plaque psoriasis. It is indicated for use in pediatric patients with polyarticular juvenile idiopathic arthritis, 2 years of age or older; juvenile psoriatic arthritis, 2 years of age or older; and plaque psoriasis, 4 years of age or older.

This pediatric postmarketing safety review was stimulated by pediatric labeling on October 18, 2023, that expanded the indication to include use in pediatric patients 2 years to 17 years old with active juvenile psoriatic arthritis.

On April 8, 2021, DPV completed a review of postmarketing adverse event reports with a serious outcome for etanercept in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with etanercept. On September 3, 2021, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

DPV reviewed all U.S. serious FAERS reports with etanercept in pediatric patients less than 18 years of age from October 1, 2020, through April 20, 2025, and identified 97 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 etanercept in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Enbrel (etanercept) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with etanercept in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Enbrel (etanercept) injection was initially approved in the U.S. on November 2, 1998. Etanercept is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis; and plaque psoriasis. It is indicated for use in pediatric patients with polyarticular juvenile idiopathic arthritis, 2 years of age or older; juvenile psoriatic arthritis, 2 years of age or older; and plaque psoriasis, 4 years of age or older.[1]

This pediatric postmarketing safety review was stimulated by pediatric labeling on October 18, 2023, that expanded the indication to include use in pediatric patients 2 years to 17 years old with active juvenile psoriatic arthritis.[2]

On April 8, 2021, DPV completed a review of postmarketing adverse event reports with a serious outcome for etanercept in pediatric patients.[3] DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with etanercept. On September 3, 2021, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

The etanercept labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional etanercept labeling information, please refer to the full prescribing information.[1]

WARNING: SERIOUS INFECTIONS and MALIGNANCIES
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCIES

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including Enbrel.**

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

- Enbrel is contraindicated in patients with sepsis.

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

- Do not start Enbrel during an active infection. If an infection develops, monitor carefully and stop Enbrel if infection becomes serious.
- Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Enbrel (those who reside or travel to regions where mycoses are endemic).
- Demyelinating disease, exacerbation or new onset, may occur.
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents.
- Congestive heart failure, worsening or new onset, may occur.
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping Enbrel.
- Monitor patients previously infected with hepatitis B virus for reactivation during and several months after therapy. If reactivation occurs, consider stopping Enbrel and beginning anti-viral therapy.
- Anaphylaxis or serious allergic reactions may occur.
- Stop Enbrel if lupus-like syndrome or autoimmune hepatitis develops.

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

- Most common adverse reactions (incidence > 5%): infections and injection site reactions.

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

8.4 Pediatric Use

Polyarticular Juvenile Idiopathic Arthritis
The safety and effectiveness of Enbrel have been established in pediatric patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (pJIA). Enbrel has been studied in 69 children with moderately to severely active pJIA 2 to 17 years of age.

The safety and effectiveness of Enbrel in pediatric patients less than 2 years of age with pJIA have not been established.

Juvenile Psoriatic Arthritis
The safety and effectiveness of Enbrel have been established in pediatric patients 2 years to 17 years old with juvenile psoriatic arthritis (JPsA). Use of Enbrel in JPsA is supported by evidence from adequate and well controlled studies of Enbrel in adults with PsA; pharmacokinetic data from adult patients with PsA, RA, and plaque psoriasis; and pharmacokinetic data from pediatric patients with active juvenile idiopathic arthritis (JIA) and plaque psoriasis. Safety of Enbrel in JPsA is supported by a clinical study in 69 pediatric patients with moderately to severely active JIA aged 2 to 17 years; a clinical study in 211 pediatric patients with moderate to severe plaque psoriasis aged 4 to 17 years; and an open-label extension study in 182 pediatric patients with moderate to severe plaque psoriasis aged 4 to 17 years.

The observed pre-dose (trough) concentrations are generally comparable between adults with RA and PsA and pediatric patients with active JIA, as well as adults with plaque psoriasis and pediatric patients with plaque psoriasis. The PK exposure is expected to be comparable between adults with PsA and pediatric patients with JPsA.

The safety and effectiveness in pediatric patients below the age of 2 years have not been established in JPsA.

Plaque Psoriasis
The safety and effectiveness of Enbrel for plaque psoriasis have been established in pediatric patients 4 years of age and older. Enbrel has been studied in 211 pediatric patients with moderate to severe plaque psoriasis aged 4 to 17 years.

The safety and effectiveness of Enbrel in pediatric patients below the age of 4 years with plaque psoriasis have not been established.

Malignancies in Pediatric Patients
Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including Enbrel.

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	April 21, 2025
Time period of search	October 1, 2020† - April 20, 2025
Search type	RxLogix Pediatric Focused Review Alert
Product terms	Product Active Ingredient: etanercept
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for etanercept ended on September 30, 2020.
‡ 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

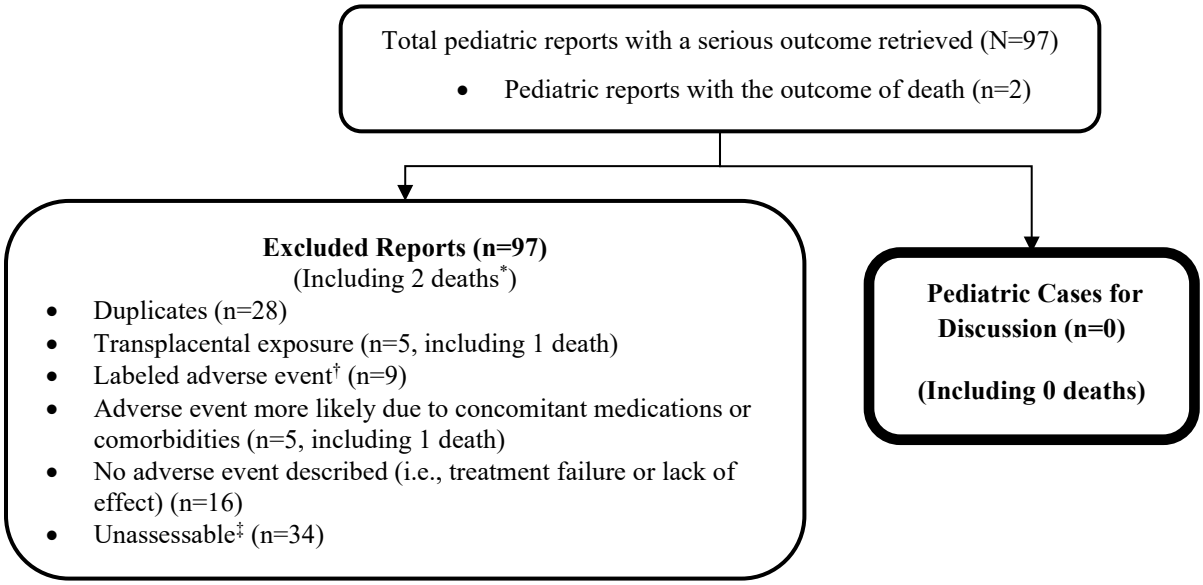
3.1 FAERS

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

Our FAERS search retrieved 97 U.S. serious pediatric reports for patients less than 18 years old from October 1, 2020, through April 20, 2025.[a] We excluded all 97 reports from the case series for the reasons listed in Figure 1.

[a] Includes one pediatric report that was identified among reports not coded with an age.

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



* Two excluded U.S. FAERS reports described fatal outcomes. One report described fetal death after prenatal exposure to etanercept; the case contained no additional details. One case described a death due to complications from underlying chronic granulomatous 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 etanercept in pediatric patients less than 18 years of age from October 1, 2020, through April 20, 2025, and identified 97 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 etanercept in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Enbrel (etanercept) injection. [package insert]. Thousand Oaks, CA. Immunex Corporation. Revised September 2024.

2. BLA 103795 Supplement Approval Letter. Accessed: May 30, 2025. Available at Drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/103795Orig1s5595ltr.pdf

3. Enbrel (etanercept) Injection. Pediatric Postmarketing Pharmacovigilance Review. April 8, 2021. Accessed: June 4, 2025. Available at: https://www.fda.gov/media/151544/download

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.