Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	March 18, 2025
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Product Name:	Aubagio (teriflunomide) tablets
Pediatric Labeling Approval Date:	April 30, 2021
Application Type/Number:	NDA 202992
Applicant:	Sanofi Aventis, U.S.
TTT Record ID:	2025-12955

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EXECUTIVE SUMMARY

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

Aubagio (teriflunomide) tablet is a pyrimidine synthesis inhibitor initially approved in the U.S. on September 12, 2012. It is currently indicated for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Aubagio is not approved for use in pediatric patients.

This pediatric postmarketing safety review was prompted by pediatric labeling on April 30, 2021, that included information on clinical studies that failed to establish safety and effectiveness for teriflunomide use in pediatric patients.

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for teriflunomide for the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with teriflunomide in pediatric patients less than 18 years of age from September 12, 2012 – January 29, 2025, and identified 11 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 teriflunomide in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Aubagio (teriflunomide) tablet is a pyrimidine synthesis inhibitor initially approved in the U.S. on September 12, 2012.[1] It is currently indicated for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[2] Aubagio is not approved for use in pediatric patients.

This pediatric postmarketing safety review was prompted by pediatric labeling on April 30, 2021, that included information on clinical studies that failed to establish safety and effectiveness for teriflunomide use in pediatric patients.[3]

DPV has not previously performed a pediatric postmarketing pharmacovigilance review for teriflunomide for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Aubagio labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Aubagio labeling information, please refer to the full prescribing information.[2]

WARNING: HEPATOTOXICITY and EMBRYOFETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Hepatotoxicity**

Clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with AUBAGIO in the postmarketing setting (5.1). Concomitant use of AUBAGIO with other hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO and monitor ALT levels at least monthly for six months (5.1). If drug induced liver injury is suspected, discontinue AUBAGIO and start accelerated elimination procedure (5.3).

- **Embryofetal Toxicity**

Teratogenicity and embryolethality occurred in animals administered teriflunomide (5.2, 8.1). Exclude pregnancy prior to initiating AUBAGIO therapy (4, 5.2, 8.1, 8.3). Advise use of effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure (4, 5.2, 5.3, 8.1, 8.3). Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant (5.2, 5.3, 8.1).

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

- Severe hepatic impairment (4, 5.1)
- Pregnancy (4, 5.2, 8.1)

- Hypersensitivity (4, 5.5)
- Current leflunomide treatment (4)

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

- Elimination of AUBAGIO can be accelerated by administration of cholestyramine or activated charcoal for 11 days. (5.3)
- AUBAGIO may decrease WBC. A recent CBC should be available before starting AUBAGIO. Monitor for signs and symptoms of infection. Consider suspending treatment with AUBAGIO in case of serious infection. Do not start AUBAGIO in patients with active infections. (5.4)
- Stop AUBAGIO if patient has anaphylaxis, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms; initiate rapid elimination. (5.3, 5.5, 5.6, 5.7)
- If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing AUBAGIO. (5.8)
- AUBAGIO may increase blood pressure. Measure blood pressure at treatment initiation and monitor blood pressure during treatment. (5.9)

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

Most common adverse reactions (≥10% and ≥2% greater than placebo): headache, diarrhea, nausea, alopecia, increase in ALT. (6)

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Effectiveness of AUBAGIO for the treatment of relapsing form of multiple sclerosis in pediatric patients (10 to 17 years of age) was not established in an adequate and well-controlled clinical study in 166 patients (109 patients received once-daily doses of AUBAGIO and 57 patients received placebo) for up to 96 weeks.

Pancreatitis has been reported in adults in the postmarketing setting, but appears to occur at higher frequency in the pediatric population. In this pediatric study, cases of pancreatitis were reported in 1.8% (2/109) of patients who received AUBAGIO compared to no patients in the placebo group. All patients in the pediatric trial recovered or were recovering after treatment discontinuation and accelerated elimination procedure [see Warnings and Precautions (5.11)].

Additionally, elevated or abnormal blood creatine phosphokinase was reported in 6.4% of pediatric patients who received AUBAGIO compared to no patients in the placebo group.

Juvenile Animal Toxicity Data

Oral administration of teriflunomide (0, 0.3, 3, or 6 mg/kg/day) to young rats on postnatal days 21 to 70 resulted in suppression of immune function (T-cell dependent antibody response) at the mid and high doses, and adverse effects on male reproductive organs (reduced sperm count) and altered neurobehavioral function (increased locomotor activity) at the high dose. At the no-effect dose (0.3 mg/kg/day) for developmental toxicity in juvenile rats, plasma exposures were less than those in pediatric patients at the doses of AUBAGIO tested in the clinical study.

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 30, 2025
Time period of search	September 12, 2012† - January 29, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Teriflunomide

Table 1. FAERS Search Strategy*	
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.
† Aubagio U.S. approval date
‡ 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

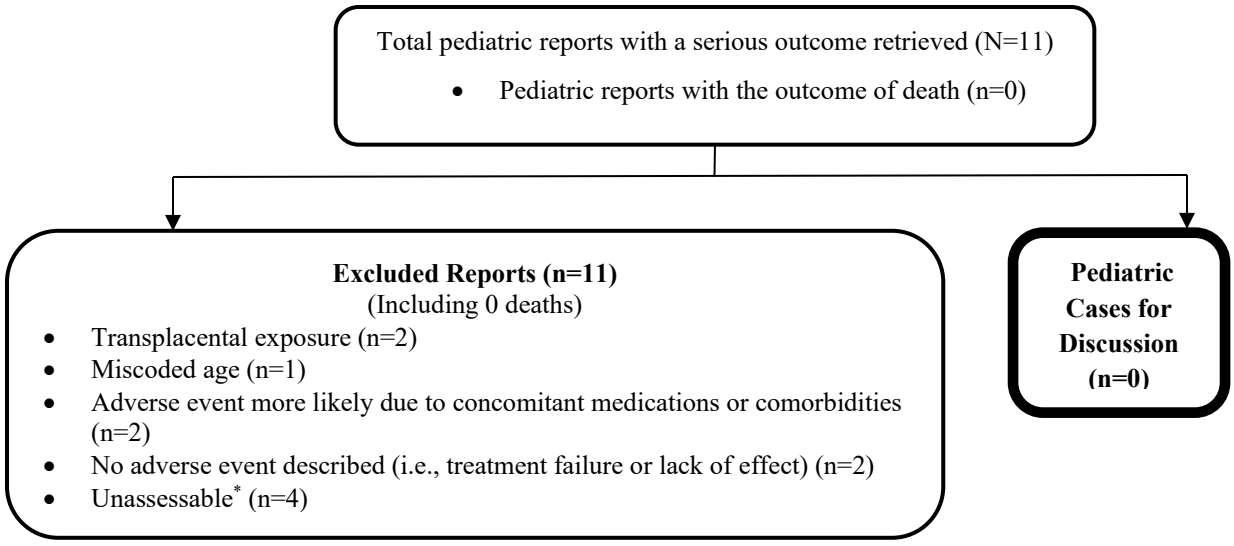
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 11 U.S. serious pediatric reports for patients less than 18 years old from September 12, 2012 – January 29, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 11 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 U.S. Serious Pediatric Cases With Teriflunomide



* 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 searched FAERS for all U.S. serious reports with teriflunomide in pediatric patients less than 18 years of age from September 12, 2012 – January 29, 2025, and identified 11 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 teriflunomide in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Aubagio (teriflunomide) tablets. [Prescribing information]. Cambridge, MA; Genzyme Corporation: September 2012.
2. Aubagio (teriflunomide) tablets. [Prescribing information]. Cambridge, MA; Genzyme Corporation: June 2024.
3. Aubagio (teriflunomide) tablets. [Prescribing information]. Cambridge, MA; Genzyme Corporation: April 2021.

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.