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 10, 2024

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Product Names	**Pediatric Labeling Approval Dates**	**Application Type/Number**	**Applicant**
Gilenya (fingolimod) capsules	May 11, 2018	NDA 022527	Novartis Pharmaceuticals Corp
Tascenso ODT (fingolimod) orally disintegrating tablet	December 23, 2021	NDA 214962	Cycle Pharmaceuticals, Ltd.

TTT Record ID: 2023-7951

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gilenya (fingolimod) capsules and Tascenso ODT (fingolimod) orally disintegrating 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) for Gilenya and PREA for Tascenso ODT. This review focuses on United States (U.S.) serious unlabeled adverse events associated with fingolimod in pediatric patients.

Gilenya (approved on September 21, 2010) and Tascenso ODT (approved on December 23, 2021) are both sphingosine 1-phosphate receptor modulators indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

This pediatric postmarketing safety review was stimulated by:

- The Gilenya pediatric labeling change on May 11, 2018, which expanded the use of Gilenya for the treatment of relapsing forms of MS in patients 10 years of age and older.

- The initial approval of Tascenso ODT, which included a pediatric indication.

DPV reviewed all U.S. serious FAERS reports for fingolimod in pediatric patients less than 18 years of age from September 21, 2010, through February 1, 2024. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with fingolimod in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gilenya (fingolimod) and Tascenso ODT (fingolimod) 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) for Gilenya and PREA for Tascenso ODT. This review focuses on United States (U.S.) serious unlabeled adverse events associated with fingolimod in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Gilenya (approved on September 21, 2010) and Tascenso ODT (approved on December 23, 2021) are both sphingosine 1-phosphate receptor modulators indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

This pediatric postmarketing safety review was stimulated by:

- The Gilenya pediatric labeling change on May 11, 2018, which expanded the use of Gilenya for the treatment of relapsing forms of MS in patients 10 years of age and older.
- The initial approval of Tascenso ODT, which included a pediatric indication.

A pediatric safety review for fingolimod has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION FOR GILENYA[1]

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

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

- Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure.
- History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker.
- Baseline QTc interval ≥500 msec.
- Treatment with Class Ia or Class III anti-arrhythmic drugs.
- Hypersensitivity to fingolimod or its excipients.

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

- Infections: GILENYA may increase the risk. Obtain a CBC before initiating treatment. Monitor for infection during treatment and for 2 months after discontinuation. Do not start in patients with active infections.
- Progressive multifocal leukoencephalopathy (PML): Withhold GILENYA at the first sign or symptom suggestive of PML.

- Macular edema: Examine the fundus before and 3–4 months after treatment start. Diabetes mellitus and uveitis increase the risk.
- Posterior reversible encephalopathy syndrome (PRES): If suspected, discontinue GILENYA.
- Respiratory effects: Evaluate when clinically indicated.
- Liver injury: Obtain liver enzyme results before initiation. Closely monitor patients with severe hepatic impairment. Discontinue if significant liver injury occurs.
- Fetal risk: Women of childbearing potential should use effective contraception during and for 2 months after stopping GILENYA.
- Increased blood pressure (BP): Monitor BP during treatment.
- Cutaneous malignancies: Suspicious skin lesions should be evaluated.

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

- Most common adverse reactions (incidence ≥10% and > placebo): Headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity.

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

8.4 Pediatric Use

Safety and effectiveness of GILENYA for the treatment of relapsing forms of multiple sclerosis in pediatric patients 10 to less than 18 years of age were established in one randomized, double-blind clinical study in 215 patients (GILENYA n=107; intramuscular interferon (IFN) beta-1a n=108).

In the controlled pediatric study, the safety profile in pediatric patients (10 to less than 18 years of age) receiving GILENYA 0.25 mg or 0.5 mg daily was similar to that seen in adult patients. In the pediatric study, cases of seizures were reported in 5.6% of GILENYA treated patients and 0.9% of interferon beta-1a treated patients.

It is recommended that pediatric patients if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating GILENYA therapy.

Safety and effectiveness of GILENYA in pediatric patients below the age of 10 years have not been established.

Juvenile Animal Toxicity Data

In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis.

When fingolimod (0.5 or 5 mg/kg/day) was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment.

Overall, a no-effect dose for adverse developmental effects in juvenile animals was not identified.

1.3 RELEVANT LABELED SAFETY INFORMATION FOR TASCENSO ODT[2]

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

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

- Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure.
- History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker.
- Baseline QTc interval ≥500 msec.
- Cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs.
- Hypersensitivity to fingolimod or its excipients.
- Concomitant use with other products containing fingolimod.

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

- Bradyarrhythmia and Atrioventricular Blocks: Because of a risk for bradyarrhythmia and AV blocks, monitor during initiation of treatment.
- Infections: TASCENSO ODT may increase the risk. Obtain a complete blood count (CBC) before initiating TASCENSO ODT (i.e., within 6 months). Monitor for infection during treatment and for 2 months after discontinuation. Do not start in patients with active infections.
- Progressive Multifocal Leukoencephalopathy (PML): Withhold TASCENSO ODT at the first sign or symptom suggestive of PML.
- Macular Edema: Examine the fundus before and 3-4 months after treatment start. Diabetes mellitus and uveitis increase the risk.
- Liver Injury: Obtain liver enzyme results before initiation and periodically during treatment. Closely monitor patients with severe hepatic impairment. Discontinue if there is evidence of liver injury without other cause.
- Posterior Reversible Encephalopathy Syndrome (PRES): If suspected, discontinue TASCENSO ODT.
- Respiratory Effects: Evaluate when clinically indicated.
- Fetal Risk: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 2 months after stopping TASCENSO ODT.

- Severe Increase in Disability After Stopping TASCENSO ODT: Monitor for development of severe increase in disability following discontinuation and begin appropriate treatment as needed.
- Tumefactive MS: Consider when severe MS relapse occurs during treatment or after discontinuation. Obtain imaging and begin treatment as needed.
- Increased Blood Pressure (BP): Monitor BP during treatment.
- Malignancies: Suspicious skin lesions should be evaluated.

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

- Most common adverse reactions (incidence ≥10% and > placebo): Headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity.

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

8.4 Pediatric Use

Safety and effectiveness of fingolimod for the treatment of relapsing forms of multiple sclerosis in pediatric patients 10 to less than 18 years of age were established in one randomized, double-blind clinical study in 215 patients (fingolimod n = 107; intramuscular interferon (IFN) beta-1a n = 108).

In the controlled pediatric study, the safety profile in pediatric patients (10 to less than 18 years of age) receiving fingolimod 0.25 mg or 0.5 mg capsules daily was similar to that seen in adult patients. In the pediatric study, cases of seizures were reported in 5.6% of fingolimod-treated patients and 0.9% of interferon beta-1a-treated patients.

It is recommended that pediatric patients, if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating TASCENSO ODT therapy.

Safety and effectiveness of TASCENSO ODT in pediatric patients below the age of 10 years have not been established.

Juvenile Animal Toxicity Data

In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis.

When fingolimod (0.5 or 5 mg/kg/day) was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment.

Overall, a no-effect dose for adverse developmental effects in juvenile animals was not identified.

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	February 2, 2024
Time period of search	September 21, 2010† - February 1, 2024
Search type	RxLogix Quick Query
Product terms	Product Active Ingredient: Fingolimod Lauryl Sulfate, Fingolimod Hydrochloride, Fingolimod
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † First U.S. approval date for fingolimod products Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

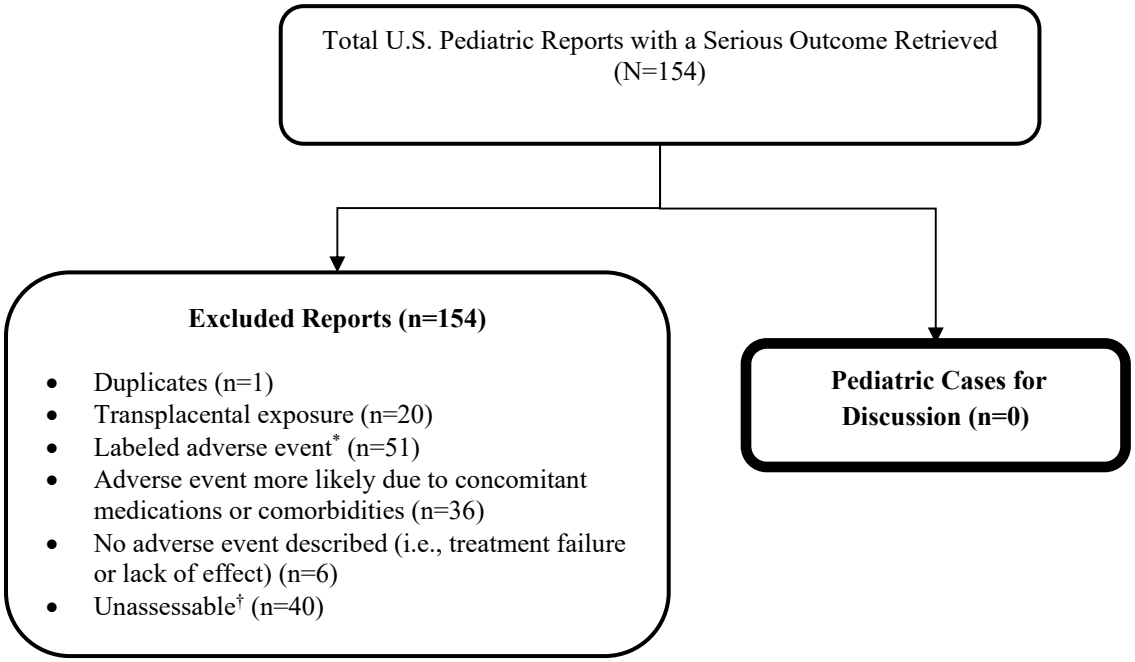
Table 2 presents the number of adult and pediatric FAERS reports from September 21, 2010, through February 1, 2024, with fingolimod.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 21, 2010 through February 1, 2024 with Fingolimod			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	46,891 (34,232)	25,861 (13,675)	689 (333)
Pediatrics (0 - < 18 years)	674 (459)	363 (154)	6 (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 154 U.S. serious pediatric reports from September 21, 2010, through February 1, 2024. All U.S. FAERS pediatric reports with a serious outcome were reviewed. We excluded all 154 reports from the case series for the reasons listed in Figure 1. We identified no U.S. serious pediatric cases for discussion.

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



*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 U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 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 fingolimod in pediatric patients less than 18 years of age from September 21, 2010, through February 1, 2024. DPV identified 154 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with fingolimod in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Gilenya (fingolimod) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. Revised August 2023.

2. Tascenso ODT (fingolimod) [package insert]. Raleigh, NC. Cycle Pharmaceuticals Ltd. c/o Icon Clinical Research LLC. Revised August 2023.

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.

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