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: September 11, 2024

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Product Names	**Pediatric Labeling Approval Dates**	**Application Type/Number**	**Applicant**
Rozlytrek (entrectinib) capsules	August 15, 2019	NDA 212726	Genentech, Inc
Rozlytrek (entrectinib) oral pellets	October 20, 2023	NDA 218550	Genentech, Inc

TTT Record ID: 2024-9605

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Rozlytrek (entrectinib) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with entrectinib in pediatric patients.

Rozlytrek (entrectinib) is a kinase inhibitor approved in the U.S. on August 15, 2019 as oral capsules. On October 20, 2023, the FDA approved Rozlytrek oral pellets, a new dosage form, and expanded the use in pediatric patients from the original approval of patients 12 years and older to patients older than 1 month of age with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation as detected by an FDA-approved test, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

Entrectinib is currently indicated for the treatment of:

● Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.

● Adult and pediatric patients older than 1 month of age with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

This pediatric postmarketing safety review was stimulated by pediatric labeling on August 15, 2019 upon FDA approval of entrectinib that included an indication for use in pediatric patients aged 12 years and older and the pediatric labeling on October 20, 2023, for entrectinib oral pellets, a new dosage form, and expanded the use in pediatric patients to patients older than 1 month of age.

DPV reviewed 10 FAERS U.S. serious reports with entrectinib in the pediatric population less than 18 years of age from August 15, 2019 through August 19, 2024. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with entrectinib. DPV did not identify any new pediatric safety concerns for entrectinib at this time.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Rozlytrek (entrectinib) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with entrectinib in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Rozlytrek (entrectinib) is a kinase inhibitor approved in the U.S. on August 15, 2019 as oral capsules. On October 20, 2023, the FDA approved Rozlytrek oral pellets, a new dosage form, and expanded the use in pediatric patients from the original approval of patients 12 years and older to patients older than 1 month of age with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation as detected by an FDA-approved test, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

Entrectinib is currently indicated for the treatment of:

● Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
● Adult and pediatric patients older than 1 month of age with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have progressed following treatment or have no satisfactory alternative therapy.

This pediatric postmarketing safety review was stimulated by pediatric labeling on August 15, 2019 upon FDA approval of entrectinib that included an indication for use in pediatric patients aged 12 years and older and the pediatric labeling on October 20, 2023, for entrectinib oral pellets, a new dosage form, and expanded the use in pediatric patients to patients older than 1 month of age.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

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

- None.

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

- Congestive Heart Failure: Assess left ventricular ejection fraction prior to initiation of ROZLYTREK in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of congestive heart failure (CHF). For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For new onset or worsening CHF, withhold ROZLYTREK, reassess LVEF and institute appropriate medical management. Reduce dose or permanently discontinue ROZLYTREK based on severity of CHF or worsening LVEF.
- Central Nervous System (CNS) Effects: CNS adverse reactions including cognitive impairment, mood disorders, dizziness, and sleep disturbances can occur with ROZLYTREK. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue ROZLYTREK based on severity.
- Skeletal Fractures: ROZLYTREK increases the risk of fractures. Promptly evaluate patients with signs or symptoms of fractures.
- Hepatotoxicity: Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue ROZLYTREK based on severity. If withheld, resume ROZLYTREK at same or reduced dose based on severity.
- Hyperuricemia: Assess serum uric acid levels prior to initiation and periodically during treatment with ROZLYTREK. Monitor patients for signs and symptoms of hyperuricemia. Initiate treatment with urate lowering medications as clinically indicated and withhold ROZLYTREK for signs and symptoms of hyperuricemia. Resume at same or reduced dose upon improvement based on severity.
- QT Interval Prolongation: Monitor patients who have or who are at risk for QTc interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment. Withhold and then resume at same or reduced dose, or permanently discontinue ROZLYTREK based on severity.
- Vision Disorders: Withhold for new visual changes or changes that interfere with activities of daily living until improvement or stabilization. Conduct an ophthalmological evaluation as appropriate. Resume at same or reduced dose upon improvement or stabilization.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

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

- The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

----------DRUG INTERACTIONS----------

- Moderate and Strong CYP3A Inhibitors:
    - For adult and pediatric patients 2 years and older, reduce the dose of ROZLYTREK if coadministration of moderate or strong CYP3A inhibitors cannot be avoided.
    - For pediatric patients less than 2 years, avoid coadministration with ROZLYTREK.
- Moderate and Strong CYP3A Inducers: Avoid coadministration with ROZLYTREK.
- Drugs That Prolong QTc Interval: Avoid concomitant use with ROZLYTREK.

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

8.4 Pediatric Use

The safety and effectiveness of ROZLYTREK have been established in pediatric patients older than 1 month of age [Clinical Studies (14.2)]. Use of ROZLYTREK in these age groups is supported by evidence from adequate and well-controlled studies of ROZLYTREK in adults and pediatric patients with additional population pharmacokinetic data demonstrating that the exposure of drug substance in pediatric patients greater than 1 month of age is expected to be in the adult range, and that the course of disease is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of ROZLYTREK in pediatric patients with ROS1-positive NSCLC have not been established.

Juvenile Animal Toxicity Data

In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Entrectinib resulted in:

- decreased body weight gain and delayed sexual maturation at doses ≥ 4 mg/kg/day (approximately 0.06 times the human exposure (AUC) at the 600 mg dose),
- deficits in neurobehavioral assessments including functional observational battery and learning and memory (at doses ≥ 8 mg/kg/day, approximately 0.14 times the human exposure at the 600 mg dose), and
- decreased femur length at doses ≥ 16 mg/kg/day (approximately 0.18 times the human exposure at the 600 mg dose).

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	August 20, 2024
Time period of search	August 15, 2019† - August 19, 2024
Search type	RxLogix Pediatric Focused Review
Product terms	Product Active Ingredient: Entrectinib Product Name: Rozlytrek
MedDRA search terms (Version 27.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Rozlytrek (entrectinib)
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 August 15, 2019, through August 19, 2024, with entrectinib.

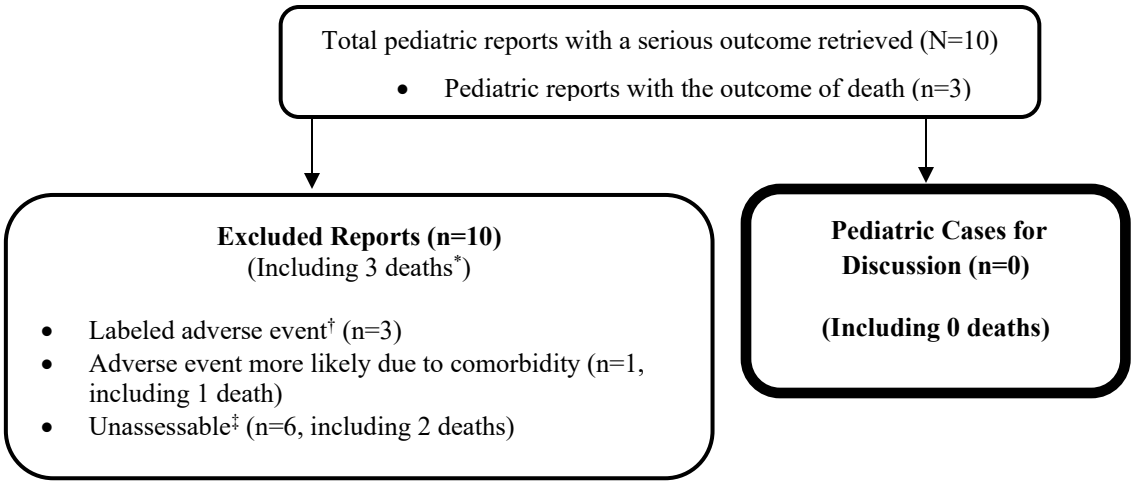
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 15, 2019 through August 19, 2024, with Entrectinib			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	597 (227)	519 (155)	117 (51)
Pediatrics (0 - < 18 years)	29‡ (11)	28‡ (10)	3‡ (3)

* 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.
‡ See Figure 1. One additional report of a U.S. pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 10 U.S. serious pediatric reports from August 15, 2019, through August 19, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 10 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 Entrectinib



* Three excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to entrectinib. One case described a male patient who received entrectinib for compassionate use died due to disease progression. The remaining two cases reported a fatal outcome but did not include sufficient clinical information to determine cause of death or causality with entrectinib.

† 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)

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

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with entrectinib in the pediatric population.

4 DISCUSSION

DPV reviewed 10 FAERS U.S. serious reports with entrectinib in the pediatric population less than 18 years of age from August 15, 2019 through August 19, 2024. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with entrectinib.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for entrectinib at this time.

6 REFERENCES

1. Rozlytrek (entrectinib) [package insert]. South San Francisco, CA. Genentech, Inc. 2024.

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.