Department of Health and Human Services
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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: May 8, 2025

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Product Name	Pediatric Labeling Approval Date	Application Type/Numbers	Applicant
Edurant (rilpivirine) tablets	March 29, 2022	NDA 202022	Janssen Research & Development, LLC
Edurant (rilpivirine) tablets	March 15, 2024	NDA 202022	Janssen Research & Development, LLC
Edurant PED (rilpivirine) tablets for suspension	March 15, 2024	NDA 219016	Janssen Research & Development, LLC

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Edurant (rilpivirine) tablets and Edurant PED (rilpivirine) tablets for oral suspension 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 rilpivirine in pediatric patients.

Edurant (rilpivirine) and Edurant PED (rilpivirine) are human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitors. Edurant is available as a tablet that contains 25 mg of rilpivirine. Edurant PED is a tablet formulation for oral suspension containing 2.5 mg of rilpivirine. Edurant was initially approved in the U.S. on May 20, 2011, and Edurant PED was initially approved on March 15, 2024.

This pediatric postmarketing safety review was prompted by pediatric labeling changes summarized below:

Labeling Date	Application Type / Numbers	Trade Name	Labeling Change
March 29, 2022	NDA 202022/0017 and 0018	Edurant	Expanded indication for use in combination with cabotegravir for treatment of HIV-1 infection in adolescents who are 12 years of age and older and weigh at least 35 kg who are virologically suppressed.
March 15, 2024	NDA 202022/0020 and 0022	Edurant	Expanded the patient population to include HIV-1 infected, treatment-naïve pediatric patients with HIV-1 RNA less than or equal to 100,000 copies/mL, who are 2 to less than 12 years of age and weigh at least 25 kg to less than 35 kg.
March 15, 2024	NDA 219016	Edurant PED	PED formulation approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL who are 2 years of age and older and weigh at least 14 kg to less than 25 kg.

DPV reviewed all U.S. serious FAERS reports with rilpivirine in pediatric patients less than 18 years of age from September 8, 2017, through April 22, 2025, and identified two reports; however, all reports were excluded from further discussion as they both described transplacental exposure to rilpivirine.

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

DPV will continue routine pharmacovigilance monitoring.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Edurant and Edurant PED (rilpivirine) 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 rilpivirine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Edurant (rilpivirine) and Edurant PED (rilpivirine) are human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitors. Edurant is available as a tablet that contains 25 mg of rilpivirine.[1] Edurant PED is a tablet formulation for oral suspension containing 2.5 mg of rilpivirine. Edurant was initially approved in the U.S. on May 20, 2011, and Edurant PED was initially approved on March 15, 2024.[1]

Edurant and Edurant PED are currently indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients 2 years of age and older and weighing at least 14 kg with HIV-1 RNA less than or equal to 100,000 copies/mL.[1] Edurant is also indicated in combination with cabotegravir, for short-term treatment of HIV-1 infection in adults and adolescents 12 years and older and weighing at least 35 kg who are virologically suppressed on a stable regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling changes summarized in **Table 1**.[2-4]

Table 1. Summary of Pediatric Related Labeling Changes for Edurant

Labeling Date	Application Numbers	Trade Name	Labeling Change
March 29, 2022	NDA 202022/0017 and 0018	Edurant	Expanded indication for use in combination with cabotegravir for treatment of HIV-1 infection in adolescents who are 12 years of age and older and weigh at least 35 kg who are virologically suppressed.
March 15, 2024	NDA 202022/0020 and 0022	Edurant	Expanded the patient population to include HIV-1 infected, treatment-naïve pediatric patients with HIV-1 RNA less than or equal to 100,000 copies/mL, who are 2 to less than 12 years of age and weigh at least 25 kg to less than 35 kg.

Table 1. Summary of Pediatric Related Labeling Changes for Edurant			
March 15, 2024	NDA 219016	Edurant PED	PED formulation approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL who are 2 years of age and older and weigh at least 14 kg to less than 25 kg.

On September 28, 2017, DPV completed a review of postmarketing adverse event reports with a serious outcome for rilpivirine-containing products, including Edurant, Complera (emtricitabine, rilpivirine, tenofovir disoproxil fumarate), and Odefsey (emtricitabine, rilpivirine, tenofovir alafenamide), in pediatric patients.[5] DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with rilpivirine-containing products. On January 7, 2018, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

----------CONTRAINDICATIONS ----------
Coadministration of EDURANT or EDURANT PED is contraindicated with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response and possible resistance and cross-resistance. (4)

----------WARNINGS AND PRECAUTIONS ----------
- Skin and Hypersensitivity Reactions: Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develop and closely monitor clinical status, including hepatic serum biochemistries. (5.1)
- Hepatotoxicity: Hepatic adverse events have been reported in patients with underlying liver disease, including hepatitis B or C virus co-infection, or in patients with elevated baseline transaminases. A few cases of hepatotoxicity have occurred in patients with no pre-existing hepatic disease. Monitor liver function tests before and during treatment with EDURANT or EDURANT PED in patients with underlying hepatic disease, such as hepatitis B or C virus co-infection, or marked elevations in transaminase. Also consider monitoring liver functions tests in patients without pre-existing hepatic dysfunction or other risk factors. (5.2)
- Depressive Disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders. (5.3)
- Patients may develop immune reconstitution syndrome. (5.5)

----------ADVERSE REACTIONS ----------
The most common adverse reactions to EDURANT or EDURANT PED (incidence >2%) of at least moderate to severe intensity (≥ Grade 2) were depressive disorders, headache, insomnia and rash. (6.1)

8.4 Pediatric Use

The safety and effectiveness of EDURANT and EDURANT PED has been established for the treatment of HIV-1 infection in treatment-naïve pediatric patients 2 years of age and older and weighing at least 14 kg. Use of EDURANT or EDURANT PED in this population is supported by three trials: TMC278-C213, TMC278HTX2002 and MOCHA.

Trial TMC278-C213

TMC278-C213 was a single arm, open-label, Phase 2 trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects, and was divided into two Cohorts.

- Cohort 1 evaluated the safety, efficacy and pharmacokinetics of EDURANT and enrolled 36 children aged 12 to less than 18 years of age and weighing at least 32 kg *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]*.
- Cohort 2 evaluated the safety, tolerability, antiviral activity and pharmacokinetics of EDURANT and EDURANT PED weight-adjusted doses 25, 15 and 12.5 mg daily, and enrolled 18 children aged 6 to less than 12 years of age and weighing at least 17 kg *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Trial TMC278HTX2002

The safety, tolerability, antiviral activity and pharmacokinetics of EDURANT and EDURANT PED weight-adjusted doses 25, 15 and 12.5 mg daily was evaluated in a single-arm, open-label Phase 2 trial in 26 HIV-1 infected pediatric subjects 2 to less than 12 years of age and weighing at least 16 kg. Trial TMC278HTX2002 supports the safety and effectiveness of EDURANT and EDURANT PED in treatment-naïve HIV-1 infected pediatric patients 2 to less than 6 years of age *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

MOCHA Trial (NCT03497676)

The safety, tolerability, and pharmacokinetics of oral and injectable cabotegravir and oral and injectable rilpivirine are being assessed in an ongoing Phase 1/2 multicenter, open-label, noncomparative study, MOCHA (IMPAACT 2017) *[see Adverse Reactions (6.1)]*. Refer to the VOCABRIA and CABENUVA prescribing information for additional information when EDURANT is used in combination with cabotegravir.

The safety and effectiveness of EDURANT in these pediatric subjects were similar to that seen in adults, and there were no significant changes on rilpivirine exposures *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness in pediatric patients less than 2 years of age or weighing less than 14 kg have not been established. Treatment with EDURANT PED is not recommended in pediatric patients less than 2 years of age or weighing below 14 kg *[see Warnings and Precautions (5.6)]*.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	April 23, 2025
Time period of search	September 8, 2017† - April 22, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: rilpivirine, rilpivirine hydrochloride
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 rilpivirine-containing products ended on September 7, 2017. ‡ 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 two U.S. serious pediatric reports for patients less than 18 years old from September 8, 2017, through April 22, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded two reports from further discussion as they both described transplacental exposure to rilpivirine.

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 rilpivirine in pediatric patients less than 18 years of age from September 8, 2017, through April 22, 2025, and identified two reports; however, all reports were excluded from further discussion as they both described transplacental exposure to rilpivirine.

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

5 CONCLUSION

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

6 REFERENCES

1. Edurant and Edurant PED (rilpivirine) [package insert]. Horsham, PA: Janssen Products, LP. March 2024.
2. U.S. Food and Drug Administration. Supplemental NDA Approval Letter (S-017, S-018) for NDA 202022, Edurant (rilpivirine). March 20, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/202022Orig1s017,s018ltr.pdf.
3. U.S. Food and Drug Administration. Supplemental NDA Approval Letter (S-020, S-022) for NDA 202022, Edurant (rilpivirine). March 15, 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/202022Orig1s020;%20s022ltr.pdf.
4. U.S. Food and Drug Administration. NDA Approval Letter for NDA 219016, Edurant PED (rilpivirine). March 15, 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/219016Orig1s000ltr.pdf.
5. Boxwell, D, Cao K, Diak IL. Edurant, Complera, Odefsey Pediatric Postmarketing Pharmacovigilance Review. September 28, 2017. Available at: https://www.fda.gov/media/110511/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.