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:	May 14, 2025
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Product Names:	Pifeltro (doravirine) and Delstrigo (doravirine, lamivudine, tenofovir disoproxil fumarate)
Pediatric Labeling Approval Date:	January 27, 2022
Application Type/Numbers:	NDA 210806 and NDA 210807
Applicant:	Merck, Sharp, & Dohme
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pifeltro (doravirine) and Desltrigo (doravirine, lamivudine, tenofovir disoproxil fumarate) 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 doravirine-containing products in pediatric patients.

Pifeltro (doravirine) is a human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitor. Delstrigo is a fixed dose combination of doravirine, lamivudine, tenofovir disoproxil fumarate. Both Pifeltro and Delstrigo were initially approved in the U.S. on August 30, 2018. Pifeltro is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg with no prior antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine. Similarly, Delstrigo is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg with no prior antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Delstrigo.

This pediatric postmarketing safety review was prompted by pediatric labeling on January 27, 2022, which expanded the indication for both products to include treatment of HIV-1 infection in pediatric patients weighing at least 35 kg and updated the *Pharmacokinetics* subsection, to include data on pharmacokinetics in pediatric patients.

DPV searched FAERS for all U.S. serious reports with doravirine-containing products in pediatric patients less than 18 years of age from August 30, 2018, through April 28, 2025, and did not identify any reports.

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

DPV will continue routine pharmacovigilance monitoring for doravirine-containing products.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pifeltro (doravirine) and Desltrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate) 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 doravirine-containing products in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Pifeltro (doravirine) is a human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitor.[1] Delstrigo is a fixed dose combination of doravirine, lamivudine, and tenofovir disoproxil fumarate.[2] Both Pifeltro and Delstrigo were initially approved in the U.S. on August 30, 2018.[1, 2] Pifeltro is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg with no prior antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine.[1] Similarly, Delstrigo is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg with no prior antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Delstrigo.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling on January 27, 2022, which expanded the indication for both products to include treatment of HIV-1 infection in pediatric patients weighing at least 35 kg and updated the *Pharmacokinetics* subsection, to include data on pharmacokinetics in pediatric patients.[3, 4]

Pediatric safety reviews for Pifeltro or Delstrigo have not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION FOR PIFELTRO

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

----------CONTRAINDICATIONS----------
- PIFELTRO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Severe skin reactions, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported during the postmarketing experience with doravirine-containing regimens. Discontinue PIFELTRO, and other medications known to be associated with severe skin reactions, immediately if a

painful rash with mucosal involvement or a progressive severe rash develops, and closely monitor clinical status. (5.1)
• Monitor for Immune Reconstitution Syndrome. (5.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams. (6.1)

---------- USE IN SPECIFIC POPULATIONS ----------
• Pediatrics: Not recommended for patients weighing less than 35 kg. (8.4)

8.4 Pediatric Use

The safety and efficacy of PIFELTRO for the treatment of HIV-1 infection have been established in pediatric patients weighing at least 35 kg *[see Indications and Usage (1) and Dosage and Administration (2.1)]*.

Use of PIFELTRO in this group is supported by evidence from adequate and well-controlled trials in adults and an open-label trial in virologically-suppressed or treatment-naïve pediatric participants 12 to less than 18 years of age. The safety, efficacy, and exposure of doravirine in these pediatric participants were similar to that in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]*.

Safety and efficacy of PIFELTRO in pediatric patients weighing less than 35 kg have not been established.

1.3 Relevant Labeled Safety Information for Delstrigo

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

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in people with concomitant HIV-1 and HBV who have discontinued lamivudine or tenofovir disoproxil fumarate (TDF), two of the components of DELSTRIGO. Closely monitor hepatic function in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)

----------CONTRAINDICATIONS----------
• DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO. (4)
• DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

---------- WARNINGS AND PRECAUTIONS ----------
• Severe skin reactions, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported during the postmarketing experience with doravirine-containing regimens. Discontinue DELSTRIGO, and other medications known to be associated with severe skin reactions, immediately if a painful rash with mucosal involvement or a progressive severe rash develops, and closely monitor clinical status. (5.1)
• New onset or worsening renal impairment: Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine

clearance, urine glucose, and urine protein in all patients. Avoid administering DELSTRIGO with concurrent or recent use of nephrotoxic drugs. (5.3)
• Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.5)
• Monitor for Immune Reconstitution Syndrome. (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams. (6.1)

---------- USE IN SPECIFIC POPULATIONS ----------
• Pediatrics: Not recommended for patients weighing less than 35 kg. (8.4)

8.4 Pediatric Use

The safety and efficacy of DELSTRIGO for the treatment of HIV-1 infection have been established in pediatric patients weighing at least 35 kg *[see Indications and Usage (1) and Dosage and Administration (2.2)]*.

Use of DELSTRIGO in this group is supported by evidence from adequate and well-controlled trials in adults with additional pharmacokinetic, safety, and efficacy data from an open-label trial in virologically-suppressed or treatment-naïve pediatric participants 12 to less than 18 years of age. The safety and efficacy of DELSTRIGO in these pediatric participants were similar to that in adults, and there was no clinically significant difference in exposure for the components of DELSTRIGO. *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]*.

Safety and efficacy of DELSTRIGO in pediatric patients weighing less than 35 kg have not been established.

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 29, 2025
Time period of search	August 30, 2018† - April 28, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: doravirine\lamivudine\tenofovir disoproxil fumarate, doravirine
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. † U.S. approval date for Pifeltro and Delstrigo ‡ 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 did not retrieve any U.S. serious pediatric reports for patients less than 18 years old from August 30, 2018, through April 28, 2025.

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 doravirine-containing products in pediatric patients less than 18 years of age from August 30, 2018, through April 28, 2025, and did not identify any reports.

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

5 CONCLUSION

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

6 REFERENCES

1. Pifeltro (doravirine) [package insert]. Rahway, NJ: Merck & Co., Inc. November 2024
2. Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate) [package insert]. Rahway, NJ: Merck & Co., Inc. November 2024
3. U.S. Food and Drug Administration. Supplemental NDA Approval Letter (S-008) for NDA 210807, Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate). January 27, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/210807Orig1s008ltr.pdf.
4. U.S. Food and Drug Administration. Supplemental NDA Approval Letter (S-007) for NDA 210806, Pifeltro (doravirine). January 27, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/210806Orig1s007ltr.pdf.

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.