**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:** | October 24, 2023 |
| **Reviewer:** | Ivone Kim, MD, Medical Officer<br>Division of Pharmacovigilance I |
| **Team Leader:** | Carmen Cheng, PharmD<br>Division of Pharmacovigilance I |
| **Division Director:** | Monica Muñoz, PharmD, PhD<br>Division of Pharmacovigilance I |
| **Product Name:** | Dutrebis (lamivudine/raltegravir) tablets |
| **Pediatric Labeling Approval Date:** | February 6, 2015 |
| **Application Type/Number:** | NDA 206510 |
| **Applicant:** | Merck Sharp & Dohme, Corp. |
| **TTT Record ID:** | 2023-6123 |

**TABLE OF CONTENTS**

## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dutrebis (lamivudine/raltegravir) tablets in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Dutrebis in pediatric patients.

Dutrebis (lamivudine/raltegravir) tablets is a fixed-dose combination product containing 150 mg of lamivudine and 300 mg of raltegravir. It was initially approved in the U.S. on February 6, 2015, for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus infection.

Of note, the Applicant for Dutrebis no longer markets the product and requested FDA withdraw approval of NDA 206510 under the process in 21 CFR 314.150(c). The withdrawal of Dutrebis from the market was effective on July 21, 2017.

This pediatric postmarketing safety review was prompted by the pediatric labeling at initial approval on February 6, 2015, that included use in pediatric patients aged 6 through 16 years and weighing at least 30 kg. A pediatric safety review for Dutrebis has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all serious reports with Dutrebis in pediatric patients less than 17 years of age from February 6, 2015 – August 28, 2023. DPV identified one report, however, the report was 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 Dutrebis in pediatric patients less than 17 years of age.

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

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dutrebis (lamivudine/raltegravir) tablets in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Dutrebis in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Dutrebis (lamivudine/raltegravir) tablet is a fixed-dose combination product containing 150 mg of lamivudine and 300 mg of raltegravir. It was initially approved in the U.S. on February 6, 2015, for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus infection.[1]

Of note, the Applicant for Dutrebis no longer markets the product and requested FDA withdraw approval of NDA 206510 under the process in 21 CFR 314.150(c). The withdrawal of Dutrebis from the market was effective on July 21, 2017.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling at initial approval on February 6, 2015, that included use in pediatric patients aged 6 through 16 years and weighing at least 30 kg. A pediatric safety review for Dutrebis has not previously been presented to the Pediatric Advisory Committee.

## 1.2 RELEVANT LABELED SAFETY INFORMATION

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

**WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY AND POST-TREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS**

***See full prescribing information for complete boxed warning***

**• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs). Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**

**• Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

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

DUTREBIS is contraindicated in patients with hypersensitivity to lamivudine, raltegravir, or any component of this medicine (4).

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

- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate (5.3).
- Severe, potentially life-threatening and fatal skin reactions have been reported, including Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis.

Discontinue treatment with DUTREBIS if signs and symptoms of severe skin reactions or severe hypersensitivity occur (5.5).
- Monitor for Immune Reconstitution Syndrome (5.6).

----------ADVERSE REACTIONS ----------
- Lamivudine: The most common reported adverse reactions (incidence ≥15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. The most common reported adverse reactions (incidence ≥15%) in pediatric patients were fever and cough (6.1).
- Raltegravir: The most common adverse reactions of moderate to severe intensity (≥2%) are insomnia, headache, dizziness, nausea and fatigue (6.1).
- Creatine kinase elevations were observed in subjects who received raltegravir. Myopathy and rhabdomyolysis have been reported (6.1).

**8.4 Pediatric Use**

DUTREBIS is indicated in pediatric patients 6 through 16 years of age and weighing at least 30 kg [see Indications and Usage (1) and Dosage and Administration (2.1)]. DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight-based dosing requirements in this patient population.

# 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 29, 2023 |
| Time period of search | February 6, 2015† - August 28, 2023 |
| Search type | RxLogix Post-Market Cases |
| Product terms | Product Active Ingredient: Lamivudine/raltegravir potassium |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database<br>† Dutrebis U.S. approval date<br>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 February 6, 2015 – August 28, 2023, with Dutrebis.

| Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 6, 2015 – August 28, 2023, With Lamivudine/Raltegravir Potassium | | | |
|---|---|---|---|
| | **All Reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 17 years) | 1 (1) | 1 (1) | 0 (0) |
| Pediatrics (0 - < 17 years) | 1 (0) | 1 (0) | 0 (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 Serious Pediatric Cases in FAERS*

Our FAERS search retrieved one serious pediatric report from February 6, 2015 – August 28, 2023. We reviewed the pediatric report with a serious outcome and excluded the report from the case series as the reported adverse event was more likely due to a concomitant medication.

### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

### *3.1.4 Summary of 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 serious reports with Dutrebis in pediatric patients less than 17 years of age from February 6, 2015 – August 28, 2023. DPV identified one report; however, the report was 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 Dutrebis in pediatric patients less than 17 years of age.

## 5 CONCLUSION

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

## 6 REFERENCES


1. Dutrebis (lamivudine and raltegravir) tablets. [Prescribing information]. Whitehouse Station, NJ; Merck Sharp & Dohme, Corp.: February, 2015.

2. Federal Register 82 FR 28322 at 28322-28329. June 21, 2017. Available at: https://www.federalregister.gov/d/2017-12908. Accessed August 30, 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.

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

IVONE E KIM
10/24/2023 11:36:53 AM

CARMEN CHENG
10/24/2023 11:52:33 AM

MONICA MUNOZ
10/24/2023 12:59:17 PM