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:	March 22, 2024
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Product Names:	Cimduo (lamivudine\tenofovir disoproxil fumarate) Temixys (lamivudine\tenofovir disoproxil fumarate)
Pediatric Labeling Approval Dates:	February 28, 2018 November 16, 2018
Application Type/Number:	NDA 022141 NDA 211284
Applicants:	Mylan Labs, LTD Celltrion Pharm, Inc.
TTT Record ID:	2023-7551

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cimduo (lamivudine\tenofovir disoproxil fumarate) and Temixys (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 lamivudine\tenofovir disoproxil fumarate in pediatric patients.

Cimduo (lamivudine\tenofovir disoproxil fumarate) is a two-drug combination of lamivudine and tenofovir disoproxil fumarate, both nucleo(t)side reverse transcriptase inhibitors. Cimduo was initially approved in the U.S. on February 28, 2018 and is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

Temixys is a two-drug combination of lamivudine and tenofovir disoproxil fumarate. Temixys was initially approved in the U.S. on November 16, 2018 and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 35 kg.

The single products Epivir (lamivudine) and Viread (tenofovir disoproxil fumarate) were initially approved in the U.S. on November 17, 1995, and October 26, 2001 respectively.

This pediatric postmarketing safety review was stimulated by pediatric labeling upon Cimduo approval on February 28, 2018, and Temixys approval on November 16, 2018. This review evaluates only those FAERS reports for the combination product lamivudine\tenofovir disoproxil fumarate.

A pediatric safety review for lamivudine\tenofovir disoproxil fumarate has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with lamivudine\tenofovir disoproxil fumarate in pediatric patients less than 18 years of age from February 28, 2018, through March 3, 2024, and did not identify any reports.

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

DPV did not identify any new pediatric safety concerns for lamivudine\tenofovir disoproxil fumarate at this time and will continue routine pharmacovigilance monitoring for lamivudine\tenofovir disoproxil fumarate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Cimduo (lamivudine\tenofovir disoproxil fumarate) and Temixys (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 lamivudine\tenofovir disoproxil fumarate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Cimduo is a two-drug combination of lamivudine and tenofovir disoproxil fumarate, both nucleo(t)side reverse transcriptase inhibitors. Cimduo was initially approved in the U.S. on February 28, 2018, and is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.[1]

Temixys is a two-drug combination of lamivudine and tenofovir disoproxil fumarate. Temixys was initially approved in the U.S. on November 16, 2018, and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 35 kg.[2] Temixys is not currently marketed in the U.S.[3]

This pediatric postmarketing safety review was stimulated by:

- The Cimduo pediatric labeling upon approval, on February 28, 2018, for the treatment of HIV-1 infection in pediatric patients weighing at least 35 kg.
- The Temixys pediatric labeling upon approval, on November 16, 2018, for the treatment of HIV-1 infection in pediatric patients weighing at least 35 kg.

The single products Epivir (lamivudine)[4] and Viread (tenofovir disoproxil fumarate)[5] were initially approved in the U.S. on November 17, 1995, and October 26, 2001, respectively. This pediatric postmarketing safety review evaluates only those FAERS reports for the combination product lamivudine\tenofovir disoproxil fumarate.

A pediatric safety review for lamivudine\tenofovir disoproxil fumarate has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION FOR CIMDUO

The Cimduo labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional lamivudine\tenofovir disoproxil fumarate labeling information, please refer to the full prescribing information.

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

- CIMDUO is contraindicated in patients with previous hypersensitivity to any of the components of this product.

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with tenofovir disoproxil fumarate, a component of CIMDUO. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with tenofovir and periodically during treatment. Avoid administering CIMDUO with concurrent or recent use of nephrotoxic drugs.
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV coinfected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue CIMDUO, as medically appropriate, and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both.
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue CIMDUO as clinically appropriate.
- Decreases in Bone Mineral Density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Immune Reconstitution Syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment.
- Redistribution/Accumulation of Body Fat: Observed in HIV-infected patients receiving antiretroviral combination therapy.
- Triple Nucleoside-Only Regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification.

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

- Most common adverse reactions (> 10% with CIMDUO) are headache, pain, depression, diarrhea, and rash.

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

8.4 Pediatric Use

The safety and effectiveness of CIMDUO as a fixed-dose tablet in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on clinical studies using the individual components (lamivudine and tenofovir disoproxil fumarate).

1.3 RELEVANT LABELED SAFETY INFORMATION FOR TEMIXYS

The Temixys labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional lamivudine\tenofovir disoproxil fumarate labeling information, please refer to the full prescribing information.

----------BOXED WARNING----------

- 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 or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate antihepatitis B treatment.

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

- TEMIXYS is contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.

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

- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported.
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering TEMIXYS with concurrent or recent use of nephrotoxic drugs.
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment.
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Lactic acidosis and severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV coinfected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue TEMIXYS as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both.
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate.

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

- Most common adverse reactions (incidence greater than 10%, with lamivudine and tenofovir disoproxil fumarate) were headache, pain, depression, diarrhea, and rash.

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

8.4 Pediatric Use

The safety and effectiveness of TEMIXYS as a fixed dose formulation in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on clinical studies using the individual components (lamivudine and tenofovir disoproxil fumarate).

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	March 4, 2024
Time period of search	February 28, 2018† - March 3, 2024
Search type	RxLogix Quick Query
Product terms	Product Active Ingredient: lamivudine\tenofovir disoproxil fumarate; lamivudine\tenofovir
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date for lamivudine\tenofovir disoproxil fumarate. 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 28, 2018, through March 3, 2024, with lamivudine\tenofovir disoproxil fumarate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 28, 2018, through March 3, 2024, With Lamivudine\Tenofovir Disoproxil Fumarate			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	79 (7)	76 (4)	6 (0)
Pediatrics (0 - < 18 years)	11 (0)	11 (0)	1 (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 Summary of U.S. Fatal Pediatric Cases in FAERS (N=0)

There are no U.S. fatal pediatric adverse event cases for discussion.

3.1.3 Selection of U.S. Serious Pediatric Cases in FAERS (N=0)

There are no non-fatal U.S. serious pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with lamivudine\tenofovir disoproxil fumarate in pediatric patients less than 18 years of age from February 28, 2018, through March 3, 2024, and did not identify any reports.

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

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for lamivudine\tenofovir disoproxil fumarate at this time and will continue routine pharmacovigilance monitoring for lamivudine\tenofovir disoproxil fumarate.

6 REFERENCES

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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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