Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	September 28, 2017
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Product Names:	Edurant® (rilpivirine) Complera® (emtricitabine, rilpivirine, tenofovir disoproxil fumarate) Odefsey® (emtricitabine, rilpivirine, tenofovir alafenamide)
Pediatric Labeling Approval Date:	Edurant®: August 26, 2015 Complera®: February 23, 2016 Odefsey®: March 1, 2016
Application Type/Sponsor/ Number:	Edurant®/Janssen/NDA 202022 Complera®/Gilead/NDA 202123 Odefsey®/Gilead/NDA 208351
OSE RCM #:	2017-1865

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for rilpivirine products in pediatric patients.

Rilpivirine (Edurant®) was first approved in 2011 and was indicated, in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adults with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy. Rilpivirine is also available in the combination products Complera® (emtricitabine, rilpivirine, and tenofovir disoproxil fumarate), approved in 2011, and Odefsey® (emtricitabine, rilpivirine, and tenofovir alafenamide), approved in 2016. Complera was indicated for use as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, or to replace a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL). Odefsey has the same indications as Complera, but Odefsey was labeled for HIV-1 infection in patients 12 years of age and older at the time of approval (2016). The indication for Edurant was expanded from adults to pediatric patients 12 years of age to less than 18 years and weighing at least 32 kg in 2015; and the indication for Complera was extended from adults to pediatric patients 12 years of age to less than 18 years weighing at least 35 kg in 2016.

There are currently no cases in the FDA Adverse Event Reporting System (FAERS) of pediatric patients who received rilpivirine (Edurant, Complera, and Odefsey). However, the Division of Pharmacovigilance will continue to monitor the FAERS database for adverse events associated with the use of rilpivirine in the pediatric population.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Edurant (rilpivirine) is available as a 25-mg tablet; Complera is available as a tablet containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate; and Odefsey is available as a tablet containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide.

Drug	Pediatric Labeling Date	BPCA or PREA	Pediatric Indication
Edurant (rilpivirine)	August 26, 2015	PREA and BPCA	HIV-1 infection in treatment-naïve pediatric patients from 12 to less than 18 years
The indication was expanded from adults to pediatric patients 12 to less than 18 years and weighing at least 32 kg. Safety, efficacy and PK were evaluated in an open-label, phase 2 trial that enrolled 36 antiretroviral treatment-naïve, HIV-1 infected pediatric patients. Information was added to Warnings and Precautions on pediatric depression: During the phase 2 trial, the incidence of depressive disorders was 19.4% (7/36). Most events were mild or moderate. The incidence of Grade 3 and 4 depressive disorders was 5.6% (2/36). Suicidal ideation and suicide attempt were reported in 1 subject. The most common ADRs reported in at least two subjects (regardless of severity) included headache (19.4%), depression (19.4%), somnolence (13.9%), nausea (11.1%), dizziness (8.3%), abdominal pain (8.3), vomiting (5.6%) and rash (5.6%).			
Complera (emtricitabine, rilpivirine, tenofovir disoproxil fumarate)	February 23, 2016	PREA	Extended the indication from adults to pediatric patients in 12 to less than 18 years
Safety and efficacy have not been established in pediatric patients less than 12 years or weighing less than 35 kg. Pediatric trials were not conducted using the emtricitabine, rilpivirine, tenofovir disoproxil fumarate fixed-dose combination tablets. Pediatric information was based on trials conducted with the individual entities.			
Odefsey (emtricitabine, rilpivirine, tenofovir alafenamide)	March 1, 2016	PREA	Treatment of HIV-1 infection in patients 12 years of age and older
Safety and efficacy of Odefsey was established in pediatric patients 12 years and older weighing 35 kg or more. Use of Odefsey in this age group is supported by adequate and well-controlled studies in adults with HIV-1 infection, and by two pediatric studies in 59 pediatric patients 12 to < 18 years. Safety and efficacy have not been established in pediatric patients less than 12 years of age or weighing less than 35 kg. Safety was similar to that observed in adults.			

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Edurant (rilpivirine)

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

Co-administration of EDURANT 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.

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

- Caution should be given to prescribing EDURANT with drugs that may reduce the exposure of rilpivirine.
- Caution should be given to prescribing EDURANT with drugs with a known risk of Torsade de Pointes.
- 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.
- Depressive Disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders.
- Hepatotoxicity: Hepatic adverse events have been reported in patients with underlying liver disease, including hepatitis B or C 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 in patients with underlying hepatic disease, such as hepatitis B or C co-infection, or marked elevations in transaminase. Also consider monitoring liver functions tests in patients without pre-existing hepatic dysfunction or other risk factors.
- Patients may develop redistribution/accumulation of body fat or immune reconstitution syndrome.

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

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

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

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk.
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission.
- Pediatrics: Safety and effectiveness have not been established in patients less than 12 years of age.

Complera (emtricitabine, rilpivirine, tenofovir disoproxil fumarate)

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

Coadministration of COMPLERA 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.

----------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). Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develops and closely monitor clinical status, including hepatic serum biochemistries.
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with COMPLERA. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose, and

urine protein before initiating treatment with COMPLERA and periodically during treatment. Avoid administering COMPLERA with concurrent or recent use of nephrotoxic drugs.
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
- Caution should be given to prescribing COMPLERA with drugs that may reduce the exposure of rilpivirine.
- Caution should be given to prescribing COMPLERA with drugs with a known risk of Torsade de Pointes.
- Depressive disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders.
- Hepatotoxicity: Hepatic adverse events have been reported in patients receiving a rilpivirine-containing regimen. Monitor liver-associated tests before and during treatment with COMPLERA in patients with underlying hepatic disease or marked elevations in liver-associated tests. Also consider monitoring liver-associated tests in patients without risk factors.
- Decreases in bone mineral density (BMD): Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.
- Coadministration with other products: Do not use with drugs containing emtricitabine, tenofovir disoproxil fumarate, or tenofovir alafenamide, including ATRIPLA, DESCOVY, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, TRUVADA, VEMLIDY, and VIREAD, or with drugs containing lamivudine. Do not administer in combination with HEPSERA. Do not coadminister in combination with rilpivirine (Edurant) unless required for dose adjustment when coadministered with rifabutin.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.

----------ADVERSE REACTIONS----------
- Most common adverse reactions to rilpivirine (incidence greater than or equal to 2%, Grades 2–4) are depressive disorders, insomnia, and headache.
- Most common adverse reactions to emtricitabine and tenofovir disoproxil fumarate (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

----------DRUG INTERACTIONS----------
- COMPLERA is a complete regimen for the treatment of HIV-1 infection; therefore, COMPLERA should not be administered with other antiretroviral medications for treatment of HIV-1 infection.
- CYP3A4 inducers or inhibitors: Drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of rilpivirine.
- Drugs that increase gastric pH: Drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk.
- Nursing mothers: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission.
- Pediatrics: Safety and effectiveness have not been established in patients less than 12 years of age.

Odefsey (emtricitabine, rilpivirine, tenofovir alafenamide)

----------CONTRAINDICATIONS----------
ODEFSEY is contraindicated when coadministered with drugs where significant decreases in RPV plasma concentrations may occur, which may result in loss of virologic response and possible resistance and cross-resistance.

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

- Skin and Hypersensitivity Reactions: Severe skin and hypersensitivity reactions have been reported during postmarketing experience with RPV-containing regimens, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develops and closely monitor clinical status, including hepatic serum biochemistries.
- Concomitant use of ODEFSEY with other drugs that may reduce the exposure of RPV may lead to loss of therapeutic effect of ODEFSEY and possible development of resistance.
- Concomitant use of ODEFSEY with drugs with a known risk to prolong the QTc interval of the electrocardiogram may increase the risk of Torsade de Pointes.
- Depressive disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders.
- Hepatotoxicity: Hepatic adverse events have been reported in patients receiving an RPV-containing regimen. Monitor liver-associated tests before and during treatment with ODEFSEY in patients with underlying hepatic disease or marked elevations in liver-associated tests. Also consider monitoring liver-associated tests in patients without risk factors.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- New onset or worsening renal impairment: Assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein is recommended before initiating ODEFSEY therapy and during therapy as clinically appropriate.
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

----------**ADVERSE REACTIONS** ----------

Most common adverse reactions (incidence greater than or equal to 2%, all grades) are headache and sleep disturbances.

----------**DRUG INTERACTIONS**----------

- CYP3A4 inducers or inhibitors: Drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of RPV.
- P-glycoprotein (P-gp) inducers or inhibitors: Drugs that strongly affect P-gp activity may lead to changes in TAF absorption.
- Drugs that increase gastric pH: Drugs that increase gastric pH may decrease plasma concentrations of RPV.

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

- Lactation: Women infected with HIV should be instructed not to breastfeed, due to the potential for HIV transmission.
- Pediatrics: Not recommended for patients less than 12 years of age or weighing less than 35 kg.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	September 7, 2017
Time Period of Search	May 20, 2011* - September 7, 2017

Reference ID: 4160242

Table 2.1.1 FAERS Search Strategy	
Search Type	Quick query
Product Names	Rilpivirine hydrochloride; rilpivirine; Edurant; Complera; Odefsey
Search Parameters	All ages, all outcomes, worldwide

* U.S. Approval date of Edurant, the first rilpivirine product approved by FDA.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports May 20, 2011 - September 7, 2017 with Rilpivirine (Edurant, Complera, Odefsey)*

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	584 (386)	355 (157)	22 (7)
Pediatrics (0 - <17 years)	8 (6)	**8‡ (6)**	0 (0)

** May include duplicates and transplacental exposures, and have not been assessed for causality*

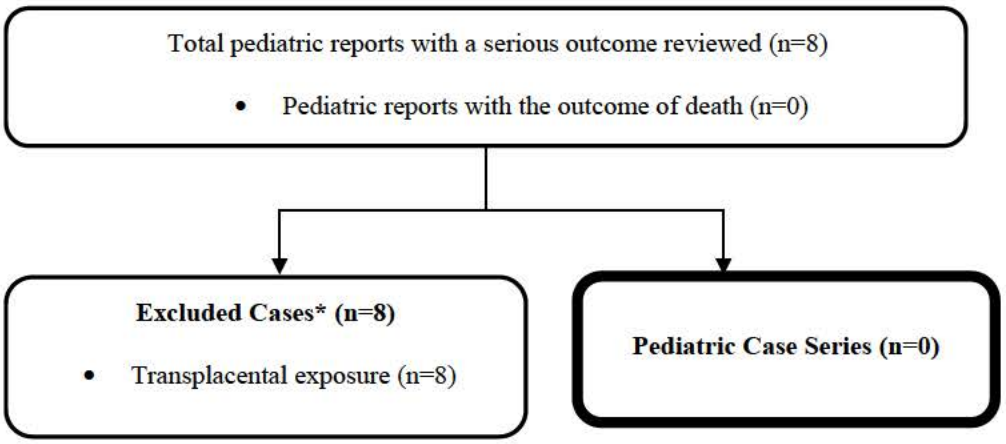
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 0 pediatric cases with a serious outcome (See **Figure 2.2.2** below).

Figure 2.2.2 Selection of Serious Pediatric Cases with Rilpivirine (Edurant, Complera, Odefsey)



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

3 DISCUSSION

There were no cases for rilpivirine (Edurant, Complera, and Odefsey) in pediatric patients, and, therefore, no safety signals were identified.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

5 RECOMMENDATIONS

The Division of Pharmacovigilance will continue to monitor the FAERS database for adverse events associated with the use of rilpivirine in the pediatric population.

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains spontaneous adverse event reports that are submitted to FDA from the product manufacturer or directly from the consumer, healthcare professional, or other reporter. The database supports the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products.

FAERS is particularly useful for identifying new (i.e., unexpected or unlabeled), rare, serious adverse events that are temporally associated with a product for which the background rate of events is low. Examples of these adverse events include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, and liver injury. Such adverse events are often not observed in the premarketing trials because these trials are limited in the number of patients, the types of patients included, and the duration of treatment. In addition, the spontaneous adverse event reports in FAERS can further refine or characterize a known adverse event.

There are inherent limitations to FAERS. FAERS data are rarely reliable for analyzing adverse events that have a delayed time to onset (e.g., effects on bone metabolism leading to osteoporosis) or a delayed time to detection (e.g., cancers). This limitation also applies to events that are not unusual in the underlying population (e.g., myocardial infarction in the older adult population). Additionally, FAERS cannot be used to quantify a risk or calculate the incidence of an adverse event because FAERS does not collect information about the total number of persons exposed to a product. Under-reporting of adverse events, as a result of the voluntary nature of spontaneous reporting, further limits the feasibility of using FAERS data to determine the incidence of an adverse event associated with a product. Because of these limitations, FAERS data should not be used to make comparisons between drugs or biologic products in an effort to identify differential risk. Specific limitations that may lead to differential reporting for one product over another may include the time the product has been on the market, publication of literature reports related to the adverse event, and publicity.

Spontaneous adverse event reports are frequently missing complete information necessary for determining whether there is a causal relationship between a product and an adverse event. For example, the reports may lack information about product exposure (e.g., timing of treatment, duration of treatment, actual dose(s) taken, or concomitant products used); baseline patient characteristics; outcomes following product dechallenge, rechallenge, or both; and information about the adverse event (e.g., relevant laboratory or radiologic information, timing, duration, and seriousness). Because of these limitations, FAERS data alone cannot often be relied upon for definitive causality determinations.

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