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Pediatric Postmarketing Pharmacovigilance

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Product Name(s): Tivicay® (dolutegravir)

**Pediatric Labeling
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Applicant/Sponsor: ViiV Healthcare

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated post-marketing adverse event reports with a serious outcome for Tivicay (dolutegravir) in pediatric patients.

NDA 204790, Tivicay (dolutegravir tablets) was initially FDA approved August 12, 2013 for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg. On June 9, 2016, FDA expanded Tivicay's approval to include pediatric patients weighing at least 30 kg.

We reviewed all serious FAERS reports for dolutegravir in the pediatric population since the drug was first approved in both children and adults from August 12, 2013 through October 10, 2017. A total of five cases were included in our case series (including two deaths). Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse event, and no deaths that were directly attributable to dolutegravir.

The reports included in the case series described adverse events that were likely due to comorbidities (e.g., pulmonary hypertensive crisis in a patient with a history of pulmonary hypertension), confounded by other diseases and medications (e.g., tubulointerstitial nephritis in a patient with renal transplant), consistent with known risks already described in labeling (i.e., pneumonia from IRIS), or had no adverse event (i.e., patient took an overdose of Tivicay). One case of pancreatitis was reported; however, this case was confounded by other medications and comorbidities known to be associated with pancreatitis. Additionally, in May 2017, dolutegravir induced pancreatitis was extensively reviewed by OSE and the conclusion was that there was no post-market safety signal. The pediatric report of pancreatitis contained in this review was also included in the previous OSE review.

Therefore, of the five cases included in this series, no specific pattern of adverse events was noted; with single reports of pneumonia, pulmonary hypertensive crisis, pancreatitis, accidental overdose, and tubulointerstitial nephritis.

There is no evidence from these data that there are any pediatric safety concerns with dolutegravir at this time. DPV recommends no regulatory action and will continue to monitor adverse events associated with the use of dolutegravir.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

NDA 204790, Tivicay (dolutegravir tablets) was initially FDA approved August 12, 2013 for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg. This indication was based on a study of 23 treatment-experienced, integrase strand transfer inhibitor (INSTI)-naïve, HIV-1 infected patients aged 12 - < 18 years in an open-label, multicenter, dose-finding clinical trial. Adverse reactions in the pediatric patients were similar to those observed in adults.

On June 9, 2016 FDA expanded Tivicay's approval to include pediatric patients weighing at least 30 kg based on results from the IMPAACT P 1093 trial, an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4-weeks to less than 18 years, in which 46 treatment-experienced INSTI-naïve subjects aged 6 to less than 18 years have been enrolled. As in prior studies involving Tivicay, adverse reactions in the pediatric patients were similar to those observed in adults. The primary safety concerns were severe hypersensitivity reactions and liver enzyme abnormalities in hepatitis B and/or hepatitis C co-infected subjects, renal and psychiatric events, all of which are included in the Tivicay label. Grade 2 adverse drug reactions (ADRs) reported by more than one subject were decrease neutrophil count (n=3) and diarrhea (n=2). There were no Grade 3 or 4 drug related ADRs reported and no ADRs led to treatment discontinuation.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

-----CONTRAINDICATIONS-----

- Previous hypersensitivity reaction to dolutegravir.(4)
- Coadministration with dofetilide. (4)

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

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY is recommended in patients with underlying hepatic disease such as hepatitis B or C. (5.2)
- Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with combination antiretroviral therapy (5.3,5.4)

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

- The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving TIVICAY in any one adult trial) are insomnia, fatigue, and headache. (6.1)

-----DRUG INTERACTIONS-----

- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, TIVICAY and supplements containing calcium or iron can be taken together with food. (7.3)

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

- Pregnancy: TIVICAY should be used during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- Lactation: Breastfeeding is not recommended. (8.2)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (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	October 10, 2017
Time Period of Search	August 12, 2013* - October 10, 2017
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Name(s)	Tivicay, dolutegravir, dolutegravir sodium
Search Parameters	All ages, all outcomes, worldwide

* U.S. Approval date in children and adults

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* August 12, 2013 - October 10, 2017 with Tivicay

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	2055 (911)	1524 (408)	138 (21)
Pediatrics (0 - <18 years)	52 (22)	49[‡] (19)	8 (2)

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

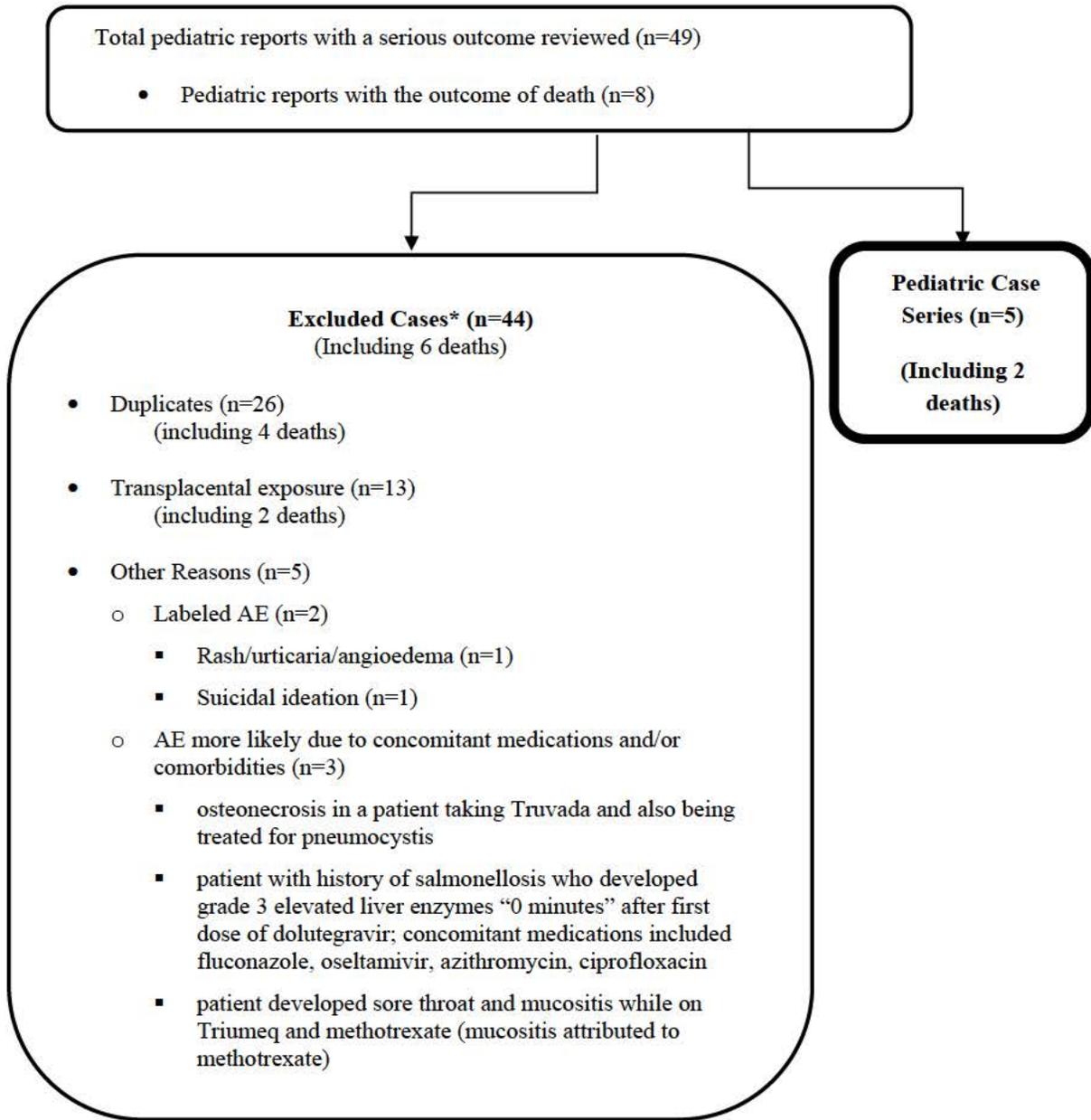
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 49 pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the cases to be summarized in **Sections 2.3 and 2.4**.

Figure 2.2.2 Selection of Serious Pediatric Cases with Tivicay



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above. Fatal cases were excluded only if it was a transplacental exposure or duplicate; all other fatal cases are described in the case series.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

2.3.1 Unlabeled Event: *Pneumonia (n=1)*

FAERS case #13664325 describes a 17-year-old adolescent girl who developed pneumonia while taking dolutegravir (Tivicay) with emtricitabine, tenofovir (Truvada) for HIV infection. The physician reported that initially the patient did not take the medication properly, however eventually, she took the medication as prescribed. Per reporter, evidence of the patient's adherence was demonstrated by her total lymphocyte count which dropped from initial values in the thousands and then subsequently decreased to 120 over a short timeframe (no units provided). In addition, shortly before hospital admission, also per reporter, the patient's viral load (VL) was in hundreds of thousands. The patient was hospitalized twice during the treatment period to assure adherence to her medications and then there was a subsequent decrease in VL to the 400s (no units provided).

On an unknown date after starting the medications, the patient experienced pneumonia requiring intensive care with mechanical ventilation. Tivicay and Truvada were continued; she received the medications during her ICU stay crushed via Percutaneous Endoscopic Gastrostomy. Her lymphocyte count subsequently rose to 380 (no additional information provided). The patient later died of multi-organ failure, cardiac failure, general physical health deterioration and pneumonia; the viral load was reportedly undetectable. An autopsy was not performed.

Reviewer's Comments: While pneumonia is not listed as a labeled adverse event for Tivicay, immune reconstitution inflammatory syndrome (IRIS) is. This case reports that the patient's VL went from hundreds of thousands to undetectable during her hospitalization and treatment with Tivicay. It is possible this patient developed IRIS with an opportunistic infection resulting in pneumonia. The patient is described as initially poorly adherent to antiretroviral therapy with high VL and low lymphocyte count. We are not given details or treatment information regarding her pneumonia, only that she required intubation and intensive care.

2.3.2 Unlabeled Event: *Pulmonary hypertensive crisis (n=1)*

FAERS case #s 13708419, 13708423 describe a 14-year-old patient of unreported sex who received dolutegravir (Tivicay) with lamivudine, abacavir, darunavir and ritonavir for antiretroviral therapy (ART). The patient's past medical history was significant for pulmonary hypertension and heart disease. The patient had previously been treated with raltegravir, abacavir, lamivudine, darunavir and ritonavir. On an unknown date, raltegravir was changed to Tivicay. On an unknown date, and at an unknown time after

starting Tivicay, lamivudine and abacavir, the patient experienced a fatal pulmonary hypertensive crisis. The reported cause of death was pulmonary hypertensive crisis.

Reviewer's Comments: This patient had a history of pulmonary hypertension and heart disease in addition to HIV. The patient was on multiple medications in addition to Tivicay. There were not many details provided in the case, and it was not clear from the case description whether any of the medications were directly responsible for the pulmonary hypertensive crisis that led to the patient's death.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=3)

2.4.1 Unlabeled Event: Pancreatitis (n=1)

FAERS case #s 10174641, 10727757, 10737237, 10749812, 11169793, 11256154; also literature¹

This case describes a 16-year-old adolescent boy who was admitted to the hospital with recurrent pneumonia. He had been treated for pneumonia 1 month previously, but his cough persisted and was associated with fever and back pain. Chest x-ray revealed bilateral lower lobe infiltrates with a small left pleural effusion. He had no history of alcohol use. He improved, and was discharged on cotrimoxazole with a plan to initiate ART as an outpatient. Four days after discharge, he was readmitted with fever and rigors. Evidence of acute kidney injury was noted (creatinine of 2.3 mg/dL), with hyponatremia (130 mmol/L) and elevated transaminases (alanine aminotransferase 167 U/L, aspartate aminotransferase 233 U/L). He was diagnosed with an adverse reaction to cotrimoxazole, which was discontinued, and he was started on atovaquone prophylaxis. After a negative HLA-B*5701 test, he was started on dolutegravir/abacavir/lamivudine. His hospital course was complicated by herpes simplex virus (HSV) esophagitis and nonspecific gastritis. Despite treatment with intravenous acyclovir, his abdominal pain worsened, and 11 days after initiating ART, he was diagnosed with acute pancreatitis (amylase 384 U/L, lipase 2189 U/L). Abdominal computed tomography (CT) demonstrated mild fullness of the pancreatic head without a focal mass. ART was discontinued. Clinical pancreatitis resolved over 3 days, with improved labs and symptom resolution. Upon clinical resolution, ART was re-initiated with elvitegravir, cobicistat, emtricitabine and tenofovir. Two months after discontinuing the initial antiretroviral regimen, amylase and lipase normalized and he was asymptomatic. He was adherent to the treatment, as reflected in the continued virologic suppression.

Reviewer's Comments: This case is confounded by the initiation of other medications (atovaquone, abacavir/lamivudine) that are labeled for pancreatitis. Although the timing of the herpes simplex and pancreatitis were not specified, HSV infection is also associated with pancreatitis². While discontinuing all medications provided a positive dechallenge, without a rechallenge with dolutegravir it is unclear whether dolutegravir was the cause of this patient's pancreatitis.

2.4.2 Unlabeled Event: Accidental overdose (n=1)

FAERS case #s 13763515, 13767602 describe a 12-year-old boy who received dolutegravir (Tivicay) with lamivudine (Epivir) and abacavir (Ziagen) for HIV infection. Initially, he started Tivicay 1 dose a day with Epivir and Ziagen each with 2 doses once a day. Thirty-four days later, the dose of Tivicay was changed to one dose twice a day, and he then experienced an overdose. Tivicay, Epivir and Ziagen were all continued with no change. Per the reporter, according to local labeling, Tivicay is labeled for once daily dosing. There were no adverse events when the patient was on Tivicay twice daily. The physician was not able to estimate seriousness of the case because the patient was under observation and no adverse events developed.

Reviewer's Comments: While this case is reported as an overdose, according to the case description, there was no reported adverse event.

2.4.3 Unlabeled Event: Tubulointerstitial nephritis (n=1)

FAERS case #s 13969308, 13990227, 14027849 describes a 12-year-old boy with a past medical history significant for kidney transplant 1 year prior to this event. On an unknown date, the patient started Triumeq (abacavir/dolutegravir/lamivudine) at an unknown dose and frequency. Concomitant medications included raltegravir and Kivexa (abacavir/lamivudine). At an unknown time after starting Triumeq, the patient experienced tubulointerstitial nephritis and increased creatinine. The action taken with Triumeq was unknown, however the Kivexa and raltegravir were discontinued; the outcome of the tubulointerstitial nephritis and creatinine increased were not reported. The patient's creatinine had been raised for the previous 6 months and a recent biopsy showed florid tubule interstitial nephritis.

Reviewer's Comments: Renal impairment is listed as a treatment emergent adverse event under section 6.1 of the dolutegravir label. Raltegravir is also labeled for renal failure under section 6.1. While it is possible that either dolutegravir or raltegravir could be the cause of the interstitial nephritis in this case, the patient also appeared to be receiving a "double dose" of abacavir and Epivir since both Triumeq and Kivexa contain these drugs. In addition, it is likely that not all the patient's concomitant medications were reported; he was undoubtedly taking additional medications (i.e., immunosuppressants) with his history of renal transplantation. It is therefore difficult to assess causality regarding dolutegravir and interstitial nephritis due to the lack of information in this case.

3 DISCUSSION

We reviewed all serious FAERS reports for dolutegravir in the pediatric population since the drug was first approved in both children and adults from August 12, 2013 through October 10,

2017. A total of five cases were included in our case series (including two deaths). Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse event, and no deaths that were directly attributable to dolutegravir.

The reports included in the case series described adverse events that were likely due to comorbidities (e.g., pulmonary hypertensive crisis in a patient with a history of pulmonary hypertension), confounded by other diseases and medications (e.g., tubulointerstitial nephritis in a patient with renal transplant), consistent with known risks already described in labeling (i.e., pneumonia from IRIS), or had no adverse event (i.e., patient took an overdose of Tivicay).

One case of pancreatitis was reported; however, this case was confounded by other medications and comorbidities known to be associated with pancreatitis. Additionally, in May 2017, dolutegravir induced pancreatitis was extensively reviewed by OSE³ and the conclusion was that there was no post-market safety signal. The pediatric report of pancreatitis contained in this review was also included in the previous OSE review.

Therefore, of the five cases included in this series, no specific pattern of adverse events was noted; with single reports of pneumonia, pulmonary hypertensive crisis, pancreatitis, accidental overdose, and tubulointerstitial nephritis.

4 CONCLUSION

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

5 RECOMMENDATIONS

DPV recommends no regulatory action at this time and will continue to monitor adverse events associated with the use of dolutegravir.

6 REFERENCES

1. Thompson AB, Wynn BA, Akerele DO, Rostad CA, Anderson EJ, Camacho-Gonzalez AF et al. Acute pancreatitis associated with dolutegravir and lamivudine/ abacavir administration. *AIDS* 2015; 29 (3):390-391.
2. Konstantinou GN, Liatsos CN, Patelaros EG, Karagiannis SS, Karnesis LI, Mavrogiannis CC. Acute pancreatitis associated with herpes simplex virus infection: report of a case and review of the literature. *Eur J Gastroenterol Hepatol.* 2009 Jan;21(1):114-6. doi: 10.1097/MEG.0b013e3283005890
3. Boxwell D. Pharmacovigilance Postmarket review of Tivicay, Triumeq and pancreatitis; Tivicay: NDA 204790 Triumeq: NDA 205551. Silver Spring, MD: FDA, CDER, OSE, DPV (US); 11 May 2017. RCM # 2017-190.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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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/s/

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