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**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

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|---|---|
| **Date:** | March 21, 2023 |
| **Reviewers:** | James M. Kidd, PharmD<br>Division of Pharmacovigilance II<br><br>Ivone Kim, MD<br>Division of Pharmacovigilance I |
| **Team Leader:** | Rachna Kapoor, PharmD, MBA<br>Division of Pharmacovigilance II |
| **Deputy Division Director:** | Ida-Lina Diak, PharmD, MS<br>Division of Pharmacovigilance II |
| **Product Names:** | Tivicay (dolutegravir tablets); Tivicay PD (dolutegravir tablets for suspension) |
| **Pediatric Labeling Approval Date:** | June 12, 2020 |
| **Application Type/Number:** | NDA 204790; NDA 213983 |
| **Applicant:** | ViiV Healthcare |
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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tivicay (dolutegravir) oral tablets and Tivicay PD (dolutegravir) tablets for oral suspension in pediatric patients through age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with dolutegravir in pediatric patients.

The FDA approved Tivicay (dolutegravir) oral tablets 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. Tivicay PD (dolutegravir) tablets for oral suspension was approved on June 12, 2020 to expand the indicated population and include pediatric patients aged at least 4 weeks and weighing at least 3kg.

All 36 pediatric reports retrieved in the FAERS search were excluded because they reported transplacental exposure or were duplicate reports. Therefore, we did not identify any new safety signals, and there were no deaths directly associated with dolutegravir.

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

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tivicay (dolutegravir) oral tablets and Tivicay PD (dolutegravir) tablets for oral suspension in pediatric patients through age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with dolutegravir in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Tivicay (dolutegravir), New Drug Application (NDA) 204790, 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.[1] This indication was based on a study of 23 treatment-experienced, integrase strand transfer inhibitor (INSTI)-naïve, HIV-1 infected patients aged 12 years to less than 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.[2] The approval was based on results from the IMPAACT P1093 trial (ClinicalTrials.gov Identifier: NCT03016533), 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.

On June 12, 2020, FDA approved Tivicay PD (dolutegravir) tablets for oral suspension and expanded the indicated population to include pediatric (treatment-naïve or experienced) patients aged at least 4 weeks and weighing at least 3 kg.[3] On the same date, the approval for Tivicay was expanded to include pediatric patients weighing at least 14 kg.[4] These approvals were granted based upon expanded data from the IMPAACT P1093 trial, which had treated 159 subjects at that time. Supporting safety data was analyzed from 97 subjects in the ODYSSEY trial (ClinicalTrials.gov Identifier: NCT02259127), an ongoing, randomized controlled trial to evaluate the efficacy and safety of dolutegravir plus two nucleos[t]ide reverse transciptase inhibitors (NRTIs) versus standard of care in HIV-infected children aged less than 18 years who are starting first-line antiretroviral therapy (ART) or switching to second-line ART. In IMPAACT P1093, Grade 3 or Grade 4 ADRs occurred in 26 subjects. Among these, the most common Grade 3 adverse events were neutropenia (12%) and anemia (5%) and the most common Grade 4 adverse event was neutropenia (2%). In ODYSSEY, neutropenia (n=2) was the only Grade 3 or 4 adverse event that occurred in more than one subject. The integrated safety

assessment of both trials concluded that comparison of the major safety outcomes did not reveal any new safety signals in both trials, and that dolutegravir had a favorable safety profile in pediatric patients as in adults.

DPV previously evaluated postmarketing adverse event reports for dolutegravir in pediatric patients for the Pediatric Advisory Committee.[5] DPV's evaluation, dated December 12, 2017, was prompted by the pediatric labeling changes on June 9, 2016, described above. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with dolutegravir. The FDA posted DPV's evaluation on FDA's Web-Posted Pediatric Safety Reviews website on March 5, 2018.

### 1.2 RELEVANT LABELED SAFETY INFORMATION[7]

4 CONTRAINDICATIONS
TIVICAY and TIVICAY PD are contraindicated in patients:
- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TIVICAY or TIVICAY PD and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or TIVICAY PD or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY and TIVICAY PD are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity
Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY or TIVICAY PD [see Adverse Reactions (6.1)]. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravircontaining regimen without pre-existing hepatic disease or other identifiable risk factors. Druginduced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Embryo-Fetal Toxicity
An ongoing observational study showed an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with TIVICAY and TIVICAY PD. Assess the risks and benefits of TIVICAY and TIVICAY PD and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.
Pregnancy testing is recommended before initiation of TIVICAY or TIVICAY PD in adolescents and adults of childbearing potential *[see Dosage and Administration (2.1)]*.

Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.
TIVICAY or TIVICAY PD may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
The concomitant use of TIVICAY or TIVICAY PD and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of TIVICAY or TIVICAY PD and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TIVICAY or TIVICAY PD; review concomitant medications during therapy with TIVICAY or TIVICAY PD; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY or TIVICAY PD. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.6 Different Formulations Are Not Interchangeable
TIVICAY and TIVICAY PD are not bioequivalent and are not interchangeable on a milligramper-milligram basis *[see Clinical Pharmacology (12.3)]*. If a pediatric patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation *[see Dosage and Administration (2.3)]*. Incorrect dosing of a given formulation may result in underdosing and loss of therapeutic effect and possible development of resistance or possible clinically significant adverse reactions from greater exposure of dolutegravir.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety, pharmacokinetics, and effectiveness of TIVICAY and TIVICAY PD were evaluated in 75 HIV-1–infected, treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent subjects aged 4 weeks to less than 18 years weighing at least 3 kg in an ongoing, open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*. Additional pharmacokinetics data were evaluated in 2 pharmacokinetic substudies in ODYSSEY, an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of TIVICAY or TIVICAY PD plus two NRTIs compared with standard of care in HIV-1– infected pediatric subjects younger than 18 years *[see Clinical Pharmacology (12.3)]*. Overall, the safety data in pediatric subjects from the IMPAACT P1093 trial were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. The pharmacokinetic parameters of TIVICAY or TIVICAY PD in pediatric subjects from IMPAACT P1093 and ODYSSEY were comparable to those of adults receiving 50 mg once daily or twice daily *[see Clinical Pharmacology (12.3)]*. The effectiveness observed in IMPAACT P1093 is comparable to that of treatment-experienced adult subjects. Safety and effectiveness of TIVICAY or TIVICAY PD have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 kg or in any pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir).

# 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 | December 9, 2022 |
| Time period of search | October 11, 2017† - December 1, 2022 |
| Search type | RxLogix PV Reports Quick Query |
| Product terms | Product Active Ingredient: dolutegravir, dolutegravir sodium, dolutegravir sodium monohydrate<br>Product Name: Tivicay, Tivicay PD |
| MedDRA search terms (Version 25.1) | All PT terms |
| * See Appendix A for a description of the FAERS database.<br>† Start date is one day after last date in previous review.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term | |

# 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 October 11, 2017, to December 1, 2022, with dolutegravir.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 11, 2017 to December 1, 2022 With Dolutegravir** | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 18 years) | 2787 (810) | 2420 (484) | 233 (72) |
| Pediatrics (0 - <18 years) | 215 (40) | **209 (36)** | **20** (4) |
| * May include duplicates and transplacental exposures, and have not been assessed for causality<br>† 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. | | | |

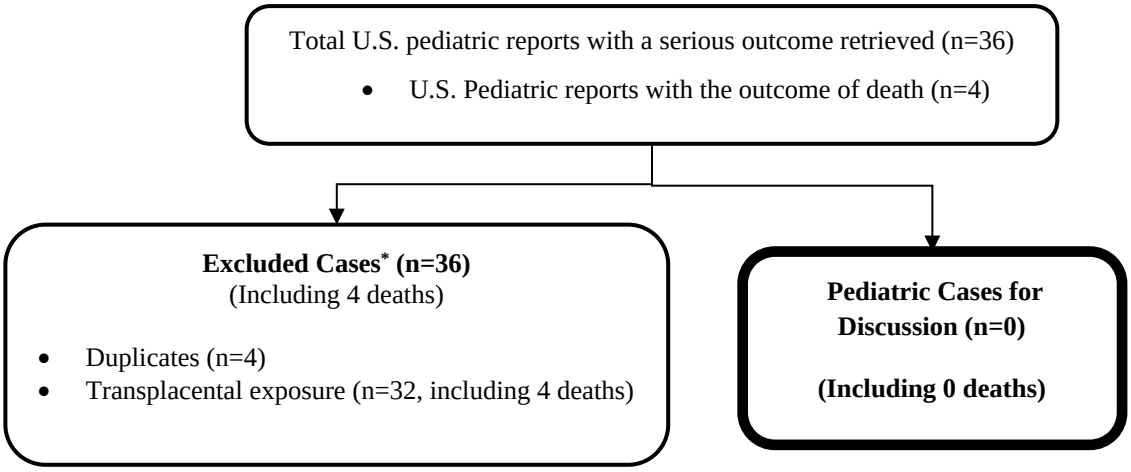
### *3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS*

Our FAERS search retrieved 36 U.S. serious pediatric reports from October 11, 2017, to December 1, 2022.

We reviewed all U.S. FAERS pediatric reports with a serious outcome and excluded all reports for the following reasons: duplicate reports (n=4) and transplacental exposure (n=32).

Figure 1 presents the selection of cases for the pediatric case series.

**Figure 1. Selection of Serious U.S. Pediatric Cases with Dolutegravir**




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

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

We identified no fatal pediatric cases with dolutegravir in the U.S. pediatric population for further discussion.

### *3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)*

We identified no serious FAERS cases with dolutegravir in the U.S. pediatric population reporting a non-fatal serious outcome.

## 4 DISCUSSION

All 36 pediatric reports retrieved in the FAERS search were excluded because they reported transplacental exposure or were duplicate reports. Therefore, we did not identify any new safety signals, and there were no deaths directly associated with dolutegravir.

## 5 CONCLUSION

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

## 6 RECOMMENDATION

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

## 7 REFERENCES


1. Food and Drug Administration. Approval Letter for NDA 204790, Tivicay (dolutegravir). August 12, 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/204790Orig1s000ltr.pdf.
2. Food and Drug Administration. Approval Letter for NDA 204790/S-008, Tivicay (dolutegravir). June 9, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/204790Orig1s008ltr.pdf.
3. Food and Drug Administration. Approval Letter for NDA 213983, Tivicay PD (dolutegravir). June 12, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213983Orig1s000ltr.pdf.
4. Food and Drug Administration. Approval Letter for NDA 204790/S-25, Tivicay (dolutegravir). June 12, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/204790Orig1s025ltr.pdf.
5. Bersoff-Matcha S, Cao K, Diak IL. Division of Pharmacovigilance Pediatric Postmarketing Pharmacovigilance Review for Tivicay. December 12, 2017.
6. Pediatric Advisory Recommendations and Updates. Available at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm510701.htm.
7. Tivicay (dolutegravir) tablets for oral use and Tivicay PD (dolutegravir) tablets for oral suspension [package insert]. Durham, NC: ViiV Healthcare. Revised October 7, 2022.

# 8 APPENDICES

## 8.1 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 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 (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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03/21/2023 12:57:26 PM

RACHNA KAPOOR
03/21/2023 12:59:48 PM

IDA-LINA DIAK
03/21/2023 01:11:14 PM