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 Review

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Product Name:	Triumeq (abacavir, dolutegravir, and lamivudine)
Pediatric Labeling Approval Date:	November 21, 2017
Application Type/Number:	NDA 205551
Applicant:	ViiV Healthcare
OSE RCM #:	2020-507

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Triumeq (abacavir, dolutegravir, and lamivudine) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all adverse events associated with Triumeq in pediatric patients.

The FDA approved Triumeq on August 22, 2014 for the treatment of HIV-1 infection in adults. On November 21, 2017, FDA approved a supplemental new drug application (sNDA) to extend the Triumeq indication to include pediatric patients weighing at least 40 kilograms (kg).

DPV reviewed all FAERS reports with Triumeq use in pediatric patients less than 18 years of age, received by FDA from August 22, 2014 through March 13, 2020. After excluding duplicate reports, transplacental exposure reports, and unassessable reports, DPV included four pediatric cases in the series.

Of the four cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Triumeq. No specific pattern of adverse events was noted; single cases of mucositis and rash were identified, along with two cases of depression (with one also reporting suicidal thoughts). These reported adverse events are consistent with the known adverse reactions described in the Triumeq labeling (i.e., rash, depression, suicidality), had limited information which precluded a meaningful causality assessment, or contained adverse events known to occur with reported concomitant medications (i.e., mucositis).

This review did not identify any new or unexpected pediatric safety concerns for Triumeq. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with Triumeq use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Triumeq (abacavir, dolutegravir, and lamivudine) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all adverse events associated with Triumeq in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Triumeq is a three-drug, fixed-dose combination (FDC) of dolutegravir (DTG), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and abacavir (ABC) and lamivudine (3TC), both of which are HIV-1 nucleoside analogue reverse transcriptase inhibitors (NRTIs). Triumeq is indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 40 kilograms (kg). Triumeq contains 600 mg of ABC, 50 mg of DTG, and 300 mg of 3TC, and is dosed at one tablet daily.[1]

On August 22, 2014, FDA first approved Triumeq for the treatment of HIV-1 infection in adults.[2] On November 21, 2017, FDA approved a supplemental new drug application (sNDA) to extend the Triumeq indication to include pediatric patients weighing at least 40 kg.[3] This sNDA was in response to PREA postmarketing requirement 2768-3: *"Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of ABC/DTG/3TC FDC tablets in HIV infected pediatric subjects 12 years to less than 18 years of age and weighing at least 40 kg. The safety and antiviral activity (efficacy) of ABC/DTG/3TC FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 to less than 18 years of age and weighing at least 40 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products."*[3]

The basis for the approval of the sNDA was the previously available data provided below for the individual drug products contained in Triumeq.[4, 5] DTG alone (Tivicay) was already approved for the treatment of HIV infection in adult and pediatric patients weighing at least 40 kg. ABC (Ziagen) and 3TC (Epivir) administered twice-daily were approved over a decade ago for the treatment of HIV infection in pediatric patients, while once daily combination ABC/3TC (Epzicom) was approved in 2015 for use in pediatric patients weighing at least 25 kg.[4]

The efficacy of the individual drug products of Triumeq was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) or the ARROW trial (NCT02028676), as summarized below.[1, 4]

- ABC and 3TC once daily, in combination with a third antiretroviral drug, were evaluated in a randomized, multicenter trial (ARROW) in HIV-1 infected, treatment-naïve subjects. Subjects randomized to once-daily dosing and who weighed at least 25 kg received ABC 600 mg and 3TC 300 mg, as either the single entities (Ziagen and Epivir) or as Epzicom. At Week 96, 67% of subjects receiving ABC and 3TC once-daily in combination with a third antiretroviral drug, had HIV-1 RNA less than 80 copies/mL. The primary safety assessment was based on severe adverse events (Grade 3 and Grade 4). One event of

Grade 4 hepatitis in the once-daily group was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related. No additional safety concerns were identified in pediatric subjects compared with historical data in adults.[1, 4]

- DTG, in combination with other antiretroviral drugs, was evaluated in treatment-experienced, INSTI-naïve, HIV-1 infected subjects aged 6 - 17 years of age in a 48-week open-label, multicenter, dose-finding clinical trial (IMPAACT P1093). Subjects aged 12 - 17 years old were enrolled in Cohort I and subjects aged 6 - 11 years old were enrolled in Cohort IIA. At 48 weeks, 61% of subjects aged 12 - 17 years treated with DTG once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies/mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% of subjects weighing at least 40 kg. The adverse event profile for DTG was similar to that for adults. Grade 2 (moderate) adverse events reported in two subjects were decreased neutrophil count; no Grade 3 or 4 adverse events were reported. Grade 3 laboratory abnormalities reported in one subject each were elevated lipase, elevated total bilirubin, and decreased white blood cell count. One Grade 4 decreased neutrophil count was identified. Any changes in mean serum creatinine were similar to those observed in adults.[1, 4]

Additionally, the bioequivalence trial (ING114580) completed with Triumeq demonstrated that the exposure from Triumeq is comparable to the exposures observed with the aforementioned individual drug products.[4]

DPV has not previously presented a Triumeq pediatric evaluation to the Pediatric Advisory Committee. This PREA review was triggered by the pediatric labeling change on November 21, 2017.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Triumeq labeling provides the following safety information (excerpted from the pertinent sections). For further Triumeq labeling information, please refer to the full prescribing information.[1]

WARNING: HYPERSENSITIVITY REACTIONS, AND EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

- Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)
- TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)
- Discontinue TRIUMEQ as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to TRIUMEQ, NEVER restart TRIUMEQ or any other abacavir-containing product. (5.1)

Exacerbations of Hepatitis B

- 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, a component of TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)

---------- **CONTRAINDICATIONS** ----------

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir, dolutegravir, or lamivudine. (4)
- Coadministration with dofetilide. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

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

- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Monitoring for hepatotoxicity is recommended. (5.4)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.5)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. An alternative treatment to TRIUMEQ should be considered at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Counsel adolescents and adults of childbearing potential to use effective contraception. (2.2, 5.6, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.8)

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

The most commonly reported adverse reactions of at least moderate intensity and incidence at least 2% (in those receiving TRIUMEQ) were insomnia, headache, and fatigue. (6.1)

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

- Pregnancy: An alternative treatment to TRIUMEQ should be considered at the time of conception through the first trimester due to the risk of neural tube defects. (2.2, 5.6, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. (8.3)
- Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)
- TRIUMEQ is not recommended in patients with creatinine clearance less than 50 mL per min. (8.6)
- If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment, then the individual components should be used. (8.7)

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

The clinical data supporting use of TRIUMEQ in HIV-1 infected pediatric patients weighing at least 40 kg is derived from the following previously conducted pediatric trials using the individual components of TRIUMEQ:

- The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of EPIVIR and ZIAGEN or EPZICOM [*see Adverse Reactions (6.2), Clinical Studies (14.2)*].
- The safety and antiviral activity (efficacy) of dolutegravir was established through a 48-week, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years were treated with dolutegravir (TIVICAY) plus optimized background therapy [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)*].

TRIUMEQ is a fixed-dose combination tablet which cannot be adjusted for patients weighing less than 40 kg [*see Clinical Pharmacology (12.3)*].

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 14, 2020
Time period of search	August 22, 2014† - March 13, 2020
Search type	FAERS Business Intelligence Solution (FBIS): Quick Query, Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient (PAI): Abacavir sulfate\dolutegravir sodium\lamivudine
MedDRA search terms (Version 22.1)	All MedDRA Preferred Terms (PTs)
* See **Appendix A** for a description of the FAERS database † U.S. approval date for Triumeq	

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 August 22, 2014 through March 13, 2020 with Triumeq.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 22, 2014 - March 13, 2020 With Triumeq

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	1746 (999)	1044 (307)	80 (25)
Pediatrics (0 - < 18 years)	63‡ (14)	62‡ (13)	34‡ (6)

* 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.

‡ See **Figure 1**. Twenty-two additional reports of pediatric deaths were identified among reports not reporting an age. The pediatric report counts reflect these 22 additional reports.

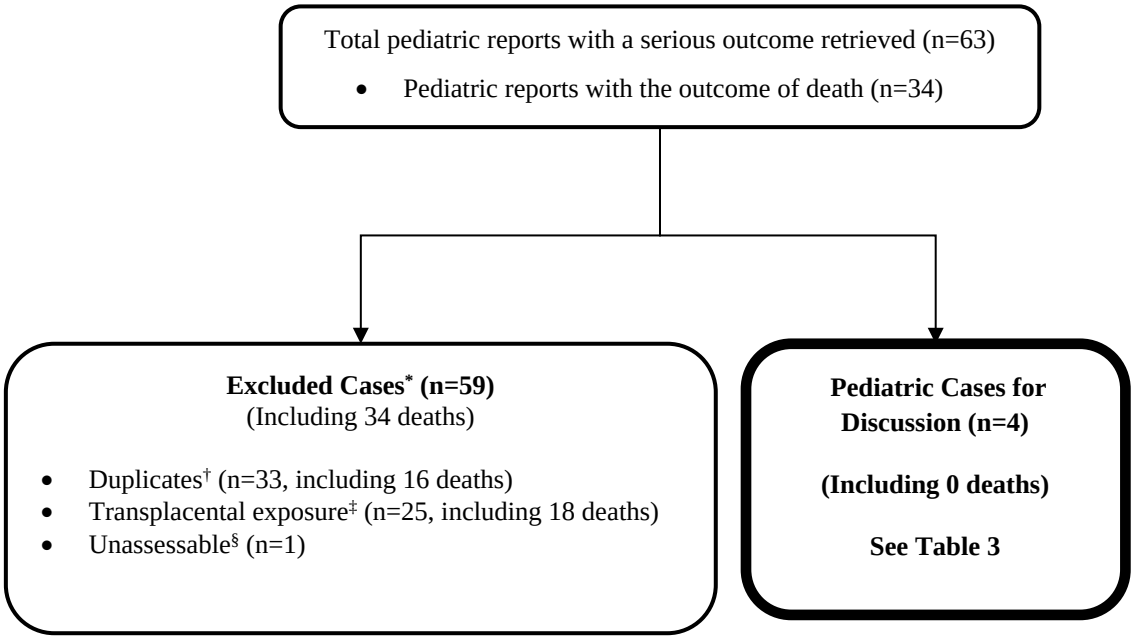
3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 63 pediatric reports from August 22, 2014 through March 13, 2020.

We reviewed all FAERS pediatric reports. We excluded reports from the case series for various reasons, such as those that were identified as duplicates (n=33), transplacental exposures (n=25), or unassessable cases (n=1). We summarize the remaining cases in the sections below.

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

Figure 1. Selection of Pediatric Cases with Triumeq



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

† Twenty-four of the 33 duplicates were duplicates of transplacental exposure cases. The remaining nine cases were duplicates of an included case.

‡ Transplacental exposures are not a focus of this review, but all transplacental reports were screened and no new safety signals were identified. Of note, FDA evaluated a safety signal of neural tube defects with transplacental exposure to dolutegravir (and products containing dolutegravir) and the labeling of these products was subsequently updated in 2019.[6, 7, 8, 9]

§ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), or the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the four pediatric cases.

Table 3 summarizes the four FAERS cases in pediatric patients with Triumeq received by FDA from August 22, 2014 through March 13, 2020.

Table 3. Characteristics of the FAERS Pediatric Cases With Triumeq Received by FDA From August 22, 2014 - March 13, 2020 (n=4)

Age	12 - < 18 years	4
Sex	Female	2
	Male	2
Country	United States	2
	Foreign	2
Reported reason for use	HIV	2
	Unknown	2
Serious outcome* (n=3)	Hospitalization	2
	Other Serious	2

* 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. A case can have more than one serious outcome.

3.1.4 Summary of Fatal Pediatric Cases (n=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.5 Summary of Non-Fatal Pediatric Cases (n=4)

We identified four FAERS cases with Triumeq in the pediatric population reporting a non-fatal outcome. These cases are summarized below.

FAERS Case # 12652027, United States, 2016, Expedited (15-Day) Report
A 16-year-old female (weight=48.6 kg) began treatment with Triumeq for HIV infection. No other information regarding medical history was reported. Concomitant medications included Abilify (aripiprazole); the reason for its use was not reported. She had been taking Abilify for approximately 1 year. After 2 weeks on Triumeq, the patient experienced depression, which progressed to suicidal thoughts. Triumeq use was continued. No information was provided regarding the disposition of Abilify.

Reviewer's Comments: This case reports the occurrence of depression and suicidal thoughts shortly after the initiation of Triumeq. The lack of information regarding medical history and

the patient's current support system, along with the concurrent use of Abilify, make the assessment of a drug-event association in this case difficult. Neuropsychiatric symptoms; including anxiety, depression, and suicidality; especially in patients with a history of psychiatric illness, have been reported in patients receiving INSTI-based regimens.[10, 11] The current Triumeq labeling contains language regarding both depression and suicidality in Section 6 - ADVERSE REACTIONS, Subsection 6.1 - Clinical Trials Experience.[1] Additionally, the Abilify labeling contains language in the BOXED WARNING and Section 5 - WARNINGS AND PRECAUTIONS regarding suicidal thought and behaviors in children, adolescents, and young adults.[12]

FAERS Case # 13790314, Ireland, 2017, Expedited (15-Day) Report
A 12-year-old female (weight not reported) began treatment with Triumeq for an unknown indication. Her medical history was significant for lymphoma. Concomitant medications included methotrexate; the reason for its use was not reported. On an unknown date, the patient experienced mucositis, sore throat, and swallowing difficulties. No information was provided regarding the disposition of Triumeq or methotrexate.

Reviewer's Comments: This case reports the occurrence of mucositis, sore throat, and swallowing difficulties an unknown time period after the initiation of Triumeq and methotrexate. Although the current Triumeq labeling contains language regarding stomatitis, which in turn could cause sore throat and swallowing difficulties, in Section 6 - ADVERSE REACTIONS, Subsection 6.2 - Postmarketing Experience, one cannot rule out the role of the concomitant use of methotrexate, which is also labeled for both mucositis and stomatitis (in the PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections).[1, 13]

FAERS Case # 15579402, United States, 2018, Non-Expedited Report
A 13-year-old male (weight not reported) began treatment with Triumeq for an unknown indication. No other information regarding medical history or concomitant medications were reported. Approximately 4 months after the initiation of Triumeq, the patient experienced a rash on both biceps that was thought to resemble ringworm. The rash was noted to be raised but not itchy. The patient had no other symptoms. No information was provided regarding the disposition of Triumeq.

Reviewer's Comments: This case reports the occurrence of a rash with no other symptoms 4 months after the initiation of Triumeq. The current Triumeq labeling contains language regarding rashes, including rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption, in Section 6 - ADVERSE REACTIONS, Subsection 6.1 - Clinical Trials Experience.[1]

FAERS Case # 16962844, Spain, 2019, Expedited (15-Day) Report
A 17-year-old male (weight not reported) began treatment with Triumeq for congenital HIV infection. No other information regarding medical history or concomitant medications were reported. Approximately 1 month after the initiation of Triumeq, the patient experienced conduct disorder and depression. Triumeq was then discontinued approximately 10 months later, and both the conduct disorder and depression were noted to be resolving.

Reviewer's Comments: This case reports the occurrence of conduct disorder and depression shortly after the initiation of Triumeq. The lack of information regarding medical history, concomitant medications, and the patient's current support system make the assessment of a drug-event association in this case difficult. In addition, neuropsychiatric symptoms; including anxiety, depression, and suicidality; especially in patients with a history of psychiatric illness, have been reported in patients receiving INSTI-based regimens.[10, 11] *The current Triumeq labeling contains language regarding depression in Section 6 - ADVERSE REACTIONS, Subsection 6.1 - Clinical Trials Experience.*[1]

4 DISCUSSION

Of the four cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Triumeq. No specific pattern of adverse events was noted; single cases of mucositis and rash were identified, along with two cases of depression (with one also reporting suicidal thoughts). These reported adverse events are consistent with the known adverse reactions described in the Triumeq labeling (i.e., rash, depression, suicidality), had limited information which precluded a meaningful causality assessment, or contained adverse events known to occur with reported concomitant medications (i.e., mucositis).

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Triumeq 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 Triumeq.

7 REFERENCES

[1] Triumeq (abacavir, dolutegravir, and lamivudine tablets) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205551s021lbl.pdf

[2] U.S. Food and Drug Administration. NDA Approval Letter for New Drug Application (NDA) 205551, Triumeq (abacavir, dolutegravir, and lamivudine), fixed-dose combination tablets, 600/50/300 mg. August 22, 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205551Orig1s000ltr.pdf (Accessed April 30, 2020).

[3] U.S. Food and Drug Administration. Supplement Approval Letter/Fulfillment of Postmarketing Requirement for NDA 205551/Supplement 11, Triumeq (abacavir, dolutegravir, and lamivudine), fixed-dose combination tablets, 600/50/300 mg. November 21, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/205551Orig1s011ltr.pdf (Accessed April 30, 2020).

[4] Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under BPCA and PREA from 2012 - Present. Medical Review for Abacavir, Dolutegravir, and Lamivudine - Triumeq. Available at https://www.fda.gov/media/109540/download (Accessed April 30, 2020).

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[6] U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). Posted May 18, 2018; Updated September 6, 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluate-potential-risk-neural-tube-birth-defects-hiv-medicine (Accessed on April 30, 2020).

[7] Triumeq (abacavir, dolutegravir, and lamivudine tablets) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised September 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205551s014s015lbl.pdf

[8] Tivicay (dolutegravir tablets) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised September 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204790s016s018lbl.pdf.

[9] Juluca (dolutegravir and rilpivirine tablets) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised September 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210192s002s004lbl.pdf

[10] U.S. Department of Health and Human Services. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV: Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Last Updated April 14, 2020. Available at: https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/PediatricGuidelines.pdf (Accessed on April 30, 2020).

[11] U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Last Updated December 18, 2019. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (Accessed on April 30, 2020).

[12] Abilify (aripiprazole tablet) [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; Updated February 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac

[13] Methotrexate tablets [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; Revised April 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	8/15/2016	12652027	1	US-VIIV HEALTHCARE LIMITED-US2016110509	Expedited (15-Day)	16	Female	USA	OT
2	7/25/2017	13790314	9	GB-VIIV HEALTHCARE LIMITED-IE2017GSK114719	Expedited (15-Day)	12	Female	IRL	HO, OT
Duplicate of 13790314		13916952	-	GB-PFIZER INC-2017368242	-	-	-	-	-
Duplicate of 13790314		13922331	-	PHFR2017IE007004	-	-	-	-	-
Duplicate of 13790314		13928087	-	PHFR2017IE007072	-	-	-	-	-
Duplicate of 13790314		13932481	-	GB-ACCORD-057863	-	-	-	-	-
Duplicate of 13790314		13947155	-	GB-TEVA-801861ACC	-	-	-	-	-
Duplicate of 13790314		13976397	-	IE-ORION CORPORATION ORION PHARMA-TREX2017-2608	-	-	-	-	-
Duplicate of 13790314		14262288	-	GB-ACCORD-061784	-	-	-	-	-
Duplicate of 13790314		14327138	-	PHHY2017IE194325	-	-	-	-	-
Duplicate of 13790314		14461435	-	GB-TEVA-2018-GB-852039	-	-	-	-	-
3	11/2/2018	15579402	1	US-VIIV HEALTHCARE LIMITED-US2018195321	Non-Expedited	13	Male	USA	-
4	10/25/2019	16962844	1	ES-VIIV HEALTHCARE LIMITED-ES2019192581	Expedited (15-Day)	17	Male	ESP	HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: ESP=Spain, HO=hospitalization, IRL=Ireland, OT=other medically significant, USA=United States of America

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