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

Date:	May 30, 2019
Safety Evaluator:	Page Crew, PharmD, MPH Division of Pharmacovigilance II
Medical Officer:	Ivone Kim, MD, FAAP Division of Pharmacovigilance I
Team Leader:	Kelly Cao, PharmD Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)
Pediatric Labeling Approval Date:	January 27, 2017
Application Type/Number:	NDA 203100
Applicant/Sponsor:	Gilead Sciences Inc.
OSE RCM #:	RCM 2019-191

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) 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 evaluates all adverse events (AEs) associated with Stribild in pediatric patients.

FDA approved Stribild oral tablets on August 27, 2012. Stribild is a combination product containing four drugs: elvitegravir (EVG), an HIV integrase strand transfer inhibitor (INSTI); cobicistat (COBI), a CYP3A inhibitor; emtricitabine (FTC), an HIV nucleoside analog reverse transcriptase inhibitor (NRTI); and tenofovir disoproxil fumarate (TDF), an HIV NRTI. Stribild is indicated as *"a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD."* The first pediatric indication for patients 12 years of age and older weighing at least 35 kg was approved on January 27, 2017.

DPV reviewed all FAERS reports with Stribild use in the pediatric population (ages zero to < 18 years), received by FDA from August 27, 2012 to January 3, 2019. After excluding duplicate reports, transplacental reports, and reports in which Stribild exposure could not be confirmed, DPV included four pediatric cases in the series. Within the case series, there were no deaths directly associated with Stribild. Of the reported unlabeled AEs, there were no new safety signals identified.

As observed in pediatric clinical trials, the safety profile for Stribild in pediatric patients appears to be similar to the safety profile of Stribild observed in adults. The most frequently reported AEs were consistent with known, labeled AEs. Among the four cases describing one or more labeled AEs, no apparent increase in severity was reported. There was no indication that the labeled AEs were occurring at increased frequency, although spontaneous databases are suboptimal for assessing frequency.

In summary, Stribild is approved for use in the pediatric population, ages 12 years and older weighing at least 35 kg. This FAERS review of AEs associated with Stribild use in pediatric patients did not identify any new safety signals. DPV recommends no regulatory action for Stribild specific to pediatric patients at this time, and will continue to monitor all AEs associated with the use of Stribild.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 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 evaluates all adverse events (AEs) associated with Stribild in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved Stribild oral tablets on August 27, 2012.[1] Stribild is a combination product containing four drugs: elvitegravir (EVG), an HIV integrase strand transfer inhibitor (INSTI); cobicistat (COBI), a CYP3A inhibitor; emtricitabine (FTC), an HIV nucleoside analog reverse transcriptase inhibitor (NRTI); and tenofovir disoproxil fumarate (TDF), an HIV NRTI.[2] Stribild is indicated as:

> *"a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD."*[2]

Stribild was initially approved for adult patients; the first pediatric indication for patients 12 years of age and older weighing at least 35 kg was approved on January 27, 2017.[1] NDA 203100/S-25 was submitted to FDA in response to PREA postmarketing requirement 1919-1[3]:

> *"Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to < 18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA [dual-energy X-ray absorptiometry] assessment).*"

One pivotal, 48-week, open-label Phase 2/3 study of Stribild in HIV-1 infected, ART-naïve adolescents provided pharmacokinetic, safety, and efficacy data to support the approved pediatric indication (Study GS-US-236-0112, NCT01721109). Per the clinical review by Dr. Mark Needles for NDA 203100/S-25[4]:

> *"Adverse events of special interest included bone, renal, and neuropsychiatric events. Bone safety was of interest because decreases in BMD [bone mineral density], increases in biochemical markers of bone metabolism, and cases of osteopenia, osteoporosis, and osteomalacia have been reported with TDF containing antiretroviral regimens. Renal safety was of interest because reports*

of proximal renal tubular dysfunction (i.e., Fanconi syndrome), increased serum creatinine, and acute renal failure have been noted with TDF use. The proximal tubule appears to be the most vulnerable to TDF-related renal injury and evidence of tubular dysfunction (i.e., proteinuria, normoglycemic glycosuria, and hypophosphatemia) may precede the decline of renal function. COBI [cobicistat] usage can lead to increased serum creatinine; however, the finding is due to inhibition of tubular secretion of creatinine and COBI is not thought to affect the actual glomerular filtration rate. Neuropsychiatric events were analyzed in the study because suicidal ideation and depression have been noted with EVG as well as other drugs in the INSTI drug class. Headache, dizziness, abnormal dreams, insomnia, depression, suicidal ideation, and suicide attempt have also been reported with STB [Stribild]."

In Study GS-US-236-0112, fifty subjects ages 12 to <18 years were enrolled, and 48 completed the study. Two subjects withdrew: one due to pregnancy and one due to non-adherence to study drug. Median age of subjects was 16 years (n=12 for ages 12-14, and n=38 for ages 15-17). Per the clinical review by Dr. Mark Needles for NDA 203100/S-25[4]:

"The majority of treatment emergent adverse events were non-serious, mild or moderate in severity, and self-limited. There were no deaths or adverse events leading to withdrawal. There was a low incidence of serious adverse events, and none of the serious adverse events were considered related to study drug. No notable changes in standard or height-age spine and total body less head (TBLH) BMD Z-scores were observed between baseline and Week 48. Median changes from baseline serum creatinine and eGFR [estimated glomerular filtration rate] were similar to those observed for adults. One subject had treatment-emergent laboratory abnormalities consistent with proximal renal tubulopathy and was ultimately lost to follow up. Overall, the adverse reaction profile in adolescents was similar to that for adults. No new or unexpected toxicities were observed."

OSE has not previously presented a Stribild pediatric evaluation to the Pediatric Advisory Committee (PAC). This PREA review was triggered by the pediatric labeling change on January 27, 2017.

1.2 SELECTED LABELED SAFETY INFORMATION

Stribild labeling provides the following safety information (excerpted from the pertinent sections). For further Stribild labeling information, please refer to full prescribing information[2].

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued EMTRIVA or VIREAD, which are components of STRIBILD. Hepatic function should be monitored closely, with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue STRIBILD. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

----------**CONTRAINDICATIONS**----------
Coadministration of STRIBILD is contraindicated with drugs that:
• Are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events. (4)
• Strongly induce CYP3A, which may lead to lower exposure of one or more components and loss of efficacy of STRIBILD and possible resistance. (4)

----------**WARNINGS AND PRECAUTIONS**----------
• New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering STRIBILD with concurrent or recent use of nephrotoxic drugs. (5.2)
• Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.3)
• Risk of adverse reactions or loss of virologic response due to drug interactions: The concomitant use of STRIBILD and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of STRIBILD and possible development of resistance; and possible clinically significant adverse reactions from greater exposures of concomitant drugs. (5.4)
• 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. (5.5)
• Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.6)

----------**ADVERSE REACTIONS**----------
Most common adverse drug reactions to STRIBILD (incidence greater than or equal to 10%, all grades) are nausea and diarrhea. (6.1)

----------**DRUG INTERACTIONS**----------
• STRIBILD is a complete regimen for the treatment of HIV-1 infection; therefore, STRIBILD should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (7.1)
• STRIBILD can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of STRIBILD. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions. (4, 7.2, 7.3, 12.3)

8.4 Pediatric Use
The pharmacokinetics, safety, and virologic and immunologic responses were evaluated in 50 treatment-naïve, HIV-1 infected subjects aged 12 to less than 18 years weighing at least 35 kg receiving STRIBILD through 48 weeks in an open-label trial (Study 112). The safety and efficacy of STRIBILD in these subjects was similar to that in antiretroviral treatment-naïve adults [see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]. Safety and effectiveness of STRIBILD in pediatric patients less than 12 years of age or weighing less than 35 kg have not been established.

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	January 4, 2019

Table 1. FAERS Search Strategy*	
Time Period of Search	August 27, 2012† - January 3, 2019
Search Type	Drug Safety Analytics Dashboard – Quick Search
Product Terms	• Product Names: Stribild, Stribild Access • Product Active Ingredients: cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate, cobicistat/elvitegravir/emtricitabine/tenofovir • NDA: 203100
MedDRA Search Terms (Version 21.1)	All Preferred Terms (PT)
Search Parameters:	Age < 18 years, all outcomes, worldwide
* See Appendix A for a description of the FAERS database. † U.S. approval date	

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 with Stribild, received by FDA from August 27, 2012 to January 3, 2019.

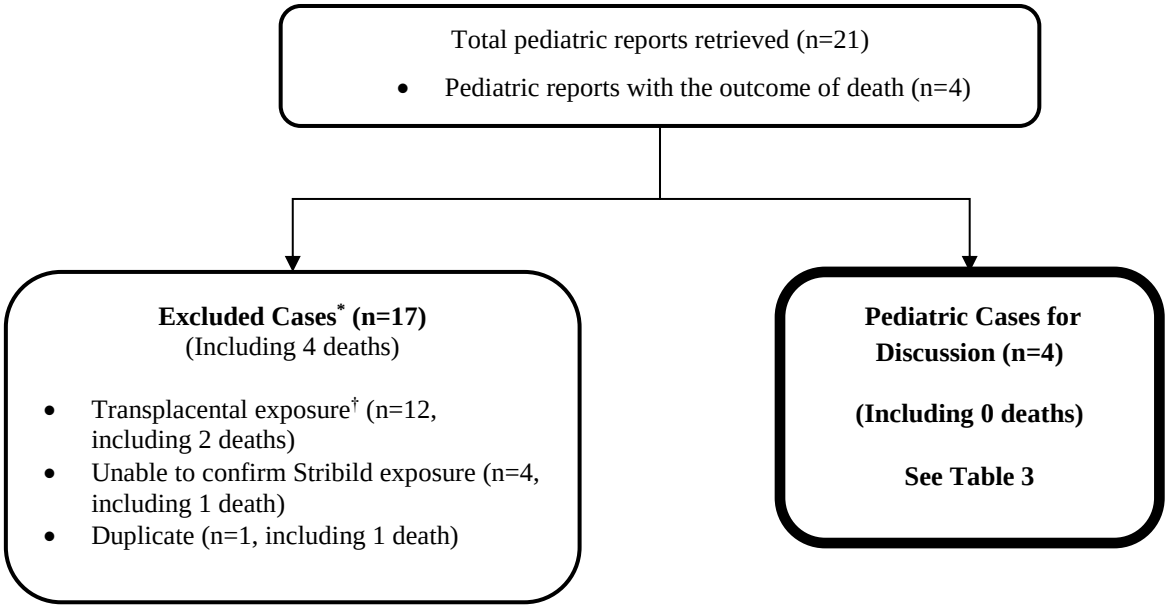
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from August 27, 2012 to January 3, 2019 with Stribild			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1284 (836)	979 (539)	45 (23)
Pediatrics (0 - <18 years)	21 (18)	19 (16)	4 (4)
* May include duplicates 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.			

3.1.2 Selection of Pediatric Cases in FAERS

The FAERS search retrieved 21 pediatric reports with Stribild, received by FDA from August 27, 2012 to January 3, 2019. Figure 1 presents the selection of cases for the pediatric case series.

We reviewed all FAERS pediatric reports, then we excluded 17 reports from the case series for the following reasons: transplacental exposure (n=12), unable to confirm Stribild exposure (n=4), and duplicate (n=1). After excluding the 17 reports as described, the series included four pediatric cases with Stribild.

Figure 1. Selection of Pediatric Cases with Stribild



* DPV reviewed all excluded cases, but they were excluded from further discussion for the reasons listed above. No new safety signals were identified among excluded cases.
† Transplacental exposures are not a focus of this review, but all transplacental reports were screened and no new safety signals were identified. FDA is currently evaluating a safety signal of transplacental exposure to dolutegravir (an INSTI) and neural tube defects (NTDs).[5] Other drugs in the INSTI class, including elvitegravir, are therefore being evaluated for this potential safety issue. Evaluation of this potential safety issue is beyond the scope of this review, but further information can be found under tracked safety issue 1898.

3.1.3 Characteristics of Pediatric Cases

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

Table 3 summarizes the four FAERS cases in pediatric patients with Stribild, received by FDA from August 27, 2012 to January 3, 2019.

Table 3. Characteristics of the FAERS Pediatric Cases with Stribild Received by FDA from August 27, 2012 to January 3, 2019

(n=4)

FAERS Case ID	Age (years); Sex	Country	Reported Reason for Use	Serious Regulatory Outcome*	Preferred Terms
10207087	17 F	USA	HIV	LT, OT	*Weight decreased, Visual impairment, Urticaria (labeled), Ulcer, Speech disorder, Rash (labeled), Paraesthesia (labeled), Insomnia (labeled), Hypoaesthesia, Fatigue (labeled), Fat redistribution, Extraocular muscle paresis, Dyspnoea (labeled), Cough (labeled), Chest discomfort, Asthenia (labeled), Anxiety (labeled)*

Table 3. Characteristics of the FAERS Pediatric Cases with Stribild Received by FDA from August 27, 2012 to January 3, 2019 (n=4)					
FAERS Case ID	**Age (years); Sex**	**Country**	**Reported Reason for Use**	**Serious Regulatory Outcome***	**Preferred Terms**
10699197	14 F	SWE	HIV	OT	*Off label use, Neutropenia (labeled)*
11650968	17 M	USA	HIV	Non-serious	*Pyrexia (labeled), Pruritus (labeled), Off label use, Musculoskeletal pain (labeled), Eye swelling, Drug interaction*
15661183	15 M	USA	NR	OT	*Pain (labeled), Osteoporosis, Emotional distress, Economic problem, Anxiety (labeled), Anhedonia*

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening (LT), hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events (OT). A case may have more than one serious outcome.
F = female; M = male; NR = not reported

3.1.4 Summary of Fatal Pediatric Cases (n=0)

We did not identify any fatal pediatric AE cases associated with Stribild in our series.[a]

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

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

FAERS Case ID#10207087 (USA)

- Case Description: A 17-year-old female started taking Stribild for HIV and experienced multiple AEs over the course of five months. Her past medical history was described as "HIV plus related issues", and she reported tobacco use. Shortly after starting Stribild, the patient developed hives, rash on upper chest/face/ears/neck, shortness of breath/difficulty breathing/wheezing, eye weakness, and fatigue. She described the events as "continuous or intermittent reactions" since starting Stribild, including depression, anxiety, mood swings, insomnia, poor appetite, poor circulation, numbness, tingling, weakness, weight loss, non-healing sores, lumps in neck, headaches, vision changes (blurred vision), cough, tightness in chest, speech impairment, dark urine, and light color stools. In response to the AEs, she stopped taking all other medications (specific medications not reported), and attributed the AEs to Stribild. She notified her primary care provider (PCP) about the rash and dark urine. The PCP prescribed an unspecified cream and assessed blood work for kidney and liver problems (results not reported). During the fourth month of Stribild therapy, the patient went to the emergency department for an unspecified reason. At the emergency department, the work-up included a chest x-ray (results not reported). At the time of the report, Stribild therapy was listed as ongoing.

[a] Among the 21 reports screened for this review, there were four reports of death. Three reports were transplacental exposures to Stribild, and in one of these reports we could not confirm exposure to Stribild. The fourth fatal report was a duplicate. No new safety signal was identified during review of these reports.

Reviewer Comments: The report describes nonspecific AEs that may represent a constellation of symptoms for several different clinical conditions. However, lack of information, particularly regarding the patient's comorbid conditions, baseline neuropsychiatric health, concomitant medications, and results of her clinical workup, limit our ability to interpret the reported AEs. This patient was also evaluated in primary care at least once and continued Stribild despite the reported AEs. In isolation, many of the AEs are labeled and consistent with the labeled events for Stribild:

- *Skin: hives, rash → labeled, and these may also represent an allergic reaction (labeled - although the patient continued Stribild despite these AEs making allergic reaction less plausible)*
- *Respiratory: shortness of breath, cough → labeled, and confounded by patient's smoking history*
- *Neuropsychiatric: headache, depression, anxiety, insomnia*
- *Other: fatigue, headaches*

Other AEs can be explained in the context of labeled events: depression (e.g., mood swings, poor appetite), anxiety (e.g., tightness in chest), and peripheral neuropathy (e.g., numbness and tingling). The dark urine/light stools are listed in Patient Information as possible signs of liver problems (labeled), but the report lacks sufficient information to determine if this patient experienced hepatic injury.

The remaining unlabeled AEs (e.g., eye weakness, vision changes (blurred vision), poor circulation, weight loss, non-healing sores, lumps in neck, speech impairment) lack sufficient information for assessment, particularly with regard to outcomes, and are challenging to interpret in the context of a single report of these AEs. In total, this case does not support a new safety signal for Stribild.

FAERS Case ID#10699197 (SWE)

- Case Description: A physician reported that a 14-year-old female started Stribild for HIV infection (previous medications not reported), then reportedly experienced neutropenia 10 months later. The patient was not receiving any other medications at the time of the AE. Outcome was not reported. Labs include:
    - Baseline/pre-Stribild: not reported
    - 10 months after starting Stribild: leukocytes = 2.38 (ref: 5-13 x10^9/L), and "unknown neutrophil granulocytes"
    - Six days later, leukocytes = 4.78, and neutrophils = 2.45 (ref: 2-8 x 10^9/L)

Reviewer Comments: Although the reporter uses the term "neutropenia", the corresponding lab values do not include a neutrophil value below the lower limit of normal according to the reported specifications. The reported leukocyte lab values suggest a slight leukopenia, but this finding is challenging to interpret without further clinical details and lab data. The narrative is lacking essential lab values for assessment, such as baseline values and trends in complete blood count, as well as HIV disease history. The patient's only medication at the time was Stribild, but the prolonged time to onset is less characteristic of a drug-induced neutropenia.[6] In addition, the narrative does not include details regarding the disposition of Stribild (continued/discontinued), particularly in the context of the reported increase in leukocytes six days after the initial lab

anomaly was identified, or details regarding the subsequent outcome. Although neutropenia has many possible non-drug-induced etiologies, the Stribild label does include a statement noting the possibility of "Grade 3/4 abnormalities of neutrophils (less than 750 per mm^3)" in Section 6.1, which have been reported in other non-Stribild clinical trials in which patients were exposed to emtricitabine or tenofovir disoproxil fumarate. As such, this case did not support a new safety signal for Stribild.

FAERS Case ID#11650968 (USA)

- Case description: A 17-year-old male with a past medical history of HIV and colitis (taking mesalamine) started taking Bactrim DS (3x/week), fluconazole, and penicillin (for syphilis). About two weeks later, he started Stribild (HIV disease/medication history not reported). Approximately 12 hours after the first Stribild dose, the patient woke up with sharp, shooting pain in the shoulder that radiated to the wrist and neck. He also experienced pruritus originating in the left upper extremity that spread to the entire body. He self-treated with diphenhydramine and ibuprofen, but when symptoms persisted he went to the emergency department. He was febrile (100.9) and had left eye swelling, which improved with diphenhydramine. Stribild disposition after the AE was not reported, and the outcome was not reported. Reported lab values (date not specified, units not specified) include:
    - ALT = 29, AST = 30, CPK=47, "CD4 lymphocytes = 8 170 cells %", C-reactive protein = 1.4, eosinophils=5, granulocytes = 86, haemoglobin=11.9, lymphocytes = 8, platelets = 162K, RBC sedimentation rate = 50; WBC count = 5
    - Treponema test = nonreactive; Viral load (virus type not reported) = 497,343; Blood and urine cultures pending

Reviewer Comments: The patient's AEs occurred following the first dose of Stribild, and about two weeks after other co-medications were introduced, which supports a temporal association with Stribild. Some symptoms (e.g., pruritus, eye swelling) may be consistent with an allergic reaction, which is labeled in Section 6.2. The report is missing important information on the patient's HIV history, past medication use, and outcomes following most of the AEs. It is difficult to understand the clinical significance of the patient's symptoms in the absence of additional information. Most of the PTs may individually reflect labeled events for Stribild: pyrexia, pruritus and pain are labeled in Section 6.1, and eye swelling may represent angioedema, which is labeled in section 6.2. In summary, this case does not support a new safety signal for Stribild.

FAERS Case ID#15661183 (USA)

- Case Description: A lawyer submitted a report describing a patient with an uncertain age – the FAERS age field was coded as 15 years but the narrative describes the patient as a "2 Decades-old Male patient". This patient was taking Truvada for one year prior to starting Stribild (other co-medications, past medical history not reported). On an unspecified date, the patient developed "weakening of the bones, pain, suffering, mental anguish, loss of enjoyment of life, lost earnings and/or a loss of earning capacity". Supportive labs were not reported. Stribild was taken for four years, but the timeline of the AEs relative to the Stribild use is unclear. The outcomes of the reported AEs (weakening of the bones, pain, suffering, mental anguish, loss of enjoyment of life) were reported as "not resolved", and the outcome for lost earnings was not reported.

Reviewer Comments: The patient in the report may be an adult, but it is possible that this patient had exposure to Stribild while < 18 years of age since the duration of Stribild therapy was four years. In the case, the reporter does not provide supportive diagnostic or laboratory findings, making the reported "weakening of the bones" and osteoporosis challenging to interpret, especially without follow-up information. The patient was exposed to TDF (in Truvada) for one year prior to starting Stribild, which may contribute to cumulative TDF toxicity. TDF has a known potential for bone toxicity, and the Stribild label notes adverse bone effects in several sections of the label, including Section 5.5 "Bone Loss and Mineralization Defects", Section 6.2 lists osteomalacia, and Section 6.1 has the following pediatric information:

> *Section 6.1 Clinical Trials in Pediatric Subjects:*
> *"Among the 50 pediatric subjects receiving STRIBILD for 48 weeks, mean BMD increased from baseline to Week 48, +0.68% at the lumbar spine and +0.77% for total body less head. Mean changes from baseline BMD Z-scores (height-age adjusted) to Week 48 were −0.09 for lumbar spine and −0.12 for total body less head. At Week 48, 7 STRIBILD subjects had significant (greater than or equal to 4%) lumbar spine BMD loss and 2 had significant total body less head BMD loss."*[2]

The other PTs, including emotional distress, anxiety, and anhedonia allude to psychiatric effects. Stribild labeling includes anxiety and depression. In summary, the narrative does not suggest any new safety signals.

4 DISCUSSION

DPV reviewed all FAERS reports with Stribild use in the pediatric population (ages zero to < 18 years), received by FDA from August 27, 2012 to January 3, 2019. After excluding duplicate reports, transplacental reports, and reports in which Stribild exposure could not be confirmed, DPV included four pediatric cases in the series. Within the case series, there were no deaths directly associated with Stribild. Of the reported unlabeled AEs, there were no new safety signals identified.

As observed in pediatric clinical trials[2], the safety profile for Stribild in pediatric patients appears to be similar to the safety profile of Stribild observed in adults. The most frequently reported AEs were consistent with known labeled AEs. Among the four cases describing one or more labeled AEs, no apparent increase in severity was reported. Although some labeled AEs are especially concerning in pediatric patients (e.g., neuropsychiatric effects, bone toxicity), these labeled AEs are described in the Stribild package insert. There was no indication that the labeled AEs were occurring at increased frequency, although spontaneous databases are suboptimal for assessing frequency. Some cases were also limited by variable data quality or lack of long-term follow up; consequently, we were unable to adequately assess for persistence of outcomes associated with labeled AEs using the available data.

In summary, Stribild is approved for use in the pediatric population, ages 12 years and older weighing at least 35 kg. This FAERS review of AEs associated with Stribild use in pediatric patients did not identify any new safety signals.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Stribild.

6 RECOMMENDATION

DPV recommends no regulatory action for Stribild specific to pediatric patients at this time, and will continue to monitor all AEs associated with the use of Stribild.

7 REFERENCES

1. U.S. Food and Drug Administration. Drugs@FDA: Stribild (NDA 203100). Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on April 12, 2019.
2. Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203100s034lbl.pdf. Accessed on April 13, 2019.
3. U.S. Food and Drug Administration. Supplement Approval/Fulfillment of Postmarketing Requirement (NDA 2031000/S-100. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on April 13, 2019.
4. Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Stribild Medical Review. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937.htm. Accessed on April 13, 2019.
5. 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). 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 May 7, 2019.
6. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007 May 1;146(9):657-65.

8 APPENDICES

8.1 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.

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	05/28/2014	10207087	1	-	DIRECT	17.57	Female	USA	LT, OT
2	01/08/2015	10699197	1	SE-GILEAD-2014-0129589	EXPEDITED	14	Female	SWE	OT
3	10/21/2015	11650968	2	US-GILEAD-2015-0177956	NON-EXPEDITED	17	Male	USA	Non-serious
4	11/27/2018	15661183	1	US-GILEAD-2018-0376103	EXPEDITED	15	Male	USA	OT

*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, or a congenital anomaly/birth defect, and 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: LT= Life-threatening, OT=Other medically significant

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAGE E CREW
05/30/2019 10:20:10 AM

IVONE E KIM
05/30/2019 10:37:04 AM

KELLY Y CAO
05/30/2019 11:19:22 AM

IDA-LINA DIAK
05/30/2019 11:35:26 AM