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:	22-May-2018
Safety Evaluator:	Paula Gish, RPh Division of Pharmacovigilance II (DPV II)
Medical Officer:	Ivone Kim, MD, FAAP Division of Pharmacovigilance I (DPV I)
Team Leader:	Kelly Cao, PharmD Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina, PharmD, MS Division of Pharmacovigilance II
Product Name:	Epivir (lamivudine)
Pediatric Labeling Approval Date:	23-Mar-2015
Application Type/Number:	NDAs 20596/032 (oral solution), 20564/033 (oral tablet)
Applicant/Sponsor:	ViiV Healthcare
OSE RCM #:	2018-477

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports with a serious outcome for lamivudine in pediatric patients.

Lamivudine was first approved in 1995 and is indicated for the treatment of HIV-1 infection in adults and pediatric patients 3 months of age and older. Lamivudine (as Epivir-HBV) is also indicated for the treatment of chronic hepatitis B virus (HBV) infection in pediatric patients 2 years of age and older.

Of the pediatric reports reviewed, there were no new safety signals, no increased severity or frequency of any labeled adverse events, no concerning use outside the approved indications, and no deaths directly attributable to lamivudine. Although we reviewed all serious FDA Adverse Event Reporting System (FAERS) reports in pediatric patients (ages 0-<17 years) received from 23-Mar-2015 (pediatric labeling date) to 11-Jan-2018, only four non-fatal cases were included in our case series. Most reports described adverse events that were attributable to concomitant medications or comorbidities (such as efavirenz-related hepatotoxicity, ataxia or seizure, abacavir or nevirapine related hypersensitivity reactions), were consistent with the known risks described in labeling (such as immune reconstitution inflammatory syndrome, gynecomastia, pancreatitis, hepatitis B reactivation following lamivudine discontinuation) or contained insufficient information to assess causality.

The four cases included in our case series described unlabeled adverse events (gastroduodenal ulcer/bleeding -1, product size issue/oropharyngeal pain/dysphagia -1, thrombocythemia-1, and gastroduodenitis-1). The cases had other plausible explanations to account for the adverse events (such as dysphagia due to methotrexate-associated mucositis), or had limited case details which precluded a meaningful causality assessment. One case of gastrointestinal ulcer with bleeding was reported with a temporal relationship to lamivudine and zidovudine use in a 7-year-old girl for non-occupational post-exposure prophylaxis. We further explored gastrointestinal ulcer as an adverse event of interest for lamivudine in all age groups. We searched all reports within the FAERS database for cases of gastrointestinal ulcer in association with lamivudine since approval. No additional compelling cases were identified.

DPV did not identify any new pediatric safety concerns with lamivudine and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of lamivudine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Epivir (lamivudine) was first approved in 1995 and is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults and pediatric patients three months of age and older. Lamivudine (as Epivir-HBV) is also indicated for the treatment of chronic hepatitis B virus (HBV) infection in pediatric patients 2 years of age and older.

Lamivudine has not been previously presented to the Pediatric Advisory Committee.

This review was prompted by pediatric labeling approved on 23-Mar-2015 that changed the dosing regimen from twice-daily to once-daily for the treatment of HIV-1 infection.

Treatment of HIV-1 infection: Epivir tablets and oral solution received accelerated approval for the treatment of HIV-1 infection (twice-daily dosing) on 17-Nov-1995. Initial pediatric approval (twice daily-dosing) for pediatric patients 3 months of age and older was approved on 23-Mar-1999. Approval for once-daily administration in adults was granted on 24-Jun-2002. Once-daily dosing in pediatric patients 3 months of age and older was approved on 23-Mar-2015.

Epivir for treatment of HIV-1 infection is supplied as 150mg film-coated tablets, 300mg film-coated tablets and 10mg/ml oral solution.

Pediatric clinical trials for treatment of HIV-1 infection include the following:

- Initial pediatric approval- Trial ACTG300 was the pivotal clinical trial for the initial 1999 approval of lamivudine use in pediatric patients for treatment of HIV-1 infection (twice-daily dosing in patients 3 months of age and older). ACTG300 was a multicenter, randomized, double-blind trial that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy in symptomatic, HIV-1 infected therapy-naïve pediatric subjects. The median age was 2.7 years (range 6 weeks to 14 years). Two hundred thirty-six patients were treated with lamivudine plus zidovudine.

  In Trial ACTG300 selected clinical adverse reactions and physical findings (greater than or equal to 5% frequency) in lamivudine plus zidovudine treated subjects included fever, hepatomegaly, nausea & vomiting, diarrhea, stomatitis, splenomegaly, cough, abnormal breath sounds/wheezing, ear symptoms, nasal discharge or congestion, skin rashes and lymphadenopathy. Selected grade 3-4 laboratory abnormalities included absolute neutrophil count < 400/mm3, hemoglobin < 7.9 g/dL, platelets < 50,000/mm3, increased liver transaminases >10 x the upper limit of normal (ULN), lipase > 2.5 x ULN, and total amylase > 2.5 x ULN.

  Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects in open-label trials (NUCA2002, and

NUCA2005) receiving lamivudine alone or in combination with other antiretroviral agents. In Trial ACTG300, pancreatitis was not observed in the 236 lamivudine plus zidovudine-treated patients, however, pancreatitis was observed in 1 subject who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 5 subjects (15%) in open-label Trial NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial ACTG300.

- Approval for once-daily dosing: The ARROW trial (COL105677) was the pivotal pediatric clinical trial for the approval of once-daily dosing of lamivudine in pediatric patients three months of age and older. The Arrow trial was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1 infected treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing lamivudine and abacavir, dosed twice daily. After a minimum of 36-weeks, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of lamivudine and abacavir, in combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW subjects, 669 participated in Randomization 3 (Twice-Daily dosing n=333, Once-daily dosing N=336)

  The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

- Use in neonates: The Epivir label includes limited short-term safety information from two small, uncontrolled trials in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control group limits assessments of causality, but it should be presumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1 infected

patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

Treatment of chronic hepatitis B virus infection: Lamivudine (as Epivir-HBV) is also indicated for the treatment of chronic hepatitis B virus (HBV) infection associated with evidence of hepatitis B viral replication and active liver inflammation in adults and pediatric patients two years of age and older. Epivir-HBV tablets (NDA 021003) and solution (NDA 021004) received initial approval for the treatment of chronic HBV infection on 8-Dec-1998. Epivir-HBV was approved for the treatment of chronic HBV infection in pediatric patients aged 2 to 17 years of age on 16-Aug-2001.

Epivir tablets and oral solution used to treat HIV-1 infection contain a higher dose of lamivudine than Epivir-HBV tablets and oral solution used to treat chronic HBV infection.

Epivir-HBV for the treatment of chronic HBV infection is supplied as 100mg film-coated tablets, and 5mg/ml oral solution.

The safety and efficacy of Epivir-HBV in pediatric patients were evaluated in a double-blind clinical trial in 286 subjects aged 2 to 17 years, who were randomized (2:1) to receive 52 weeks of Epivir-HBV or placebo. All subjects had compensated chronic hepatitis B accompanied by evidence of hepatitis B virus replication and persistently elevated serum ALT levels. Adverse events were similar to those in adult trials. Posttreatment transaminase elevations were observed in some subjects after cessation of Epivir-HBV.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The Epivir USPI[1] includes the following information under HIGHLIGHTS:

BOXED WARNING:

WARNING: EXACERBATIONS OF HEPATITIS B, and DIFFERENT FORMULATIONS OF EPIVIR

See full prescribing information for complete boxed warning

- **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 EPIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment.**
- **Patients with HIV-1 infection should receive only dosage forms of EPIVIR appropriate for treatment of HIV-1.**

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

EPIVIR is contraindicated in patients with previous hypersensitivity reaction to lamivudine.

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

Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.

Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue EPIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both.

Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy.

Lower virologic suppression rates and increased risk of viral resistance were observed in pediatric subjects who received EPIVIR oral solution concomitantly with other antiretroviral oral solutions compared with those who received tablets. An all-tablet regimen should be used when possible.

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

The most common reported adverse reactions (incidence greater than or equal to 15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough.

The most common reported adverse reactions (incidence greater than or equal to 15%) in pediatric subjects were fever and cough.

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

Sorbitol: Coadministration of lamivudine and sorbitol may decrease lamivudine concentrations; when possible, avoid chronic coadministration.

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

Lactation: Women infected with HIV should be instructed not to breastfeed due to potential for HIV transmission.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

Table 1 FAERS Search Strategy	
Date of Search	11-Jan-2018
Time Period of Search	23-Mar-2015* – 11-Jan-2018
Search Type	FBIS profile (product manufacturer reporting summary) quick query
Product Names	Product name: Epivir, Epivir-HBV, Combivir, Trizivir, Epzicom, Triumeq, Dutrebis Product active ingredient: lamivudine, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, abacavir sulfate/dolutegravir sodium/lamivudine, lamivudine/raltegravir sodium Active ingredient: lamivudine
Search Parameters	All ages, all outcomes, worldwide, MedDRA version 20.1

** 23-Mar-2015 is the pediatric labeling date.*

Furthermore, we used Empirica Signal to perform disproportionality analyses on all reported drug event combinations for lamivudine since product approval for all pediatric and adult FAERS reports. Disproportionality analyses identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases (e.g., FAERS). Conducting disproportionality analyses complements our routine assessment of spontaneous adverse event report data. Data mining scores do not, by themselves, demonstrate causal associations; rather, they serve as a signal for further investigation.

Appendix B provides a description of data mining of FAERS using Empirica Signal.

3 RESULTS

3.1 TOTAL NUMBER OF FAERS REPORTS BY AGE

Table 2 Total Adult and Pediatric FAERS Reports* 23-Mar-2015 to 11-Jan-2018 with Lamivudine

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	4433 (985)	3818 (425)	295 (29)
Pediatrics (0 - <17 years)	446 (62)	**442‡ (58)**	43 (11)

Table 2 Total Adult and Pediatric FAERS Reports* 23-Mar-2015 to 11-Jan-2018 with Lamivudine

** 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 1.

3.2 DISPROPORTIONALITY ANALYSES OF FAERS REPORTS

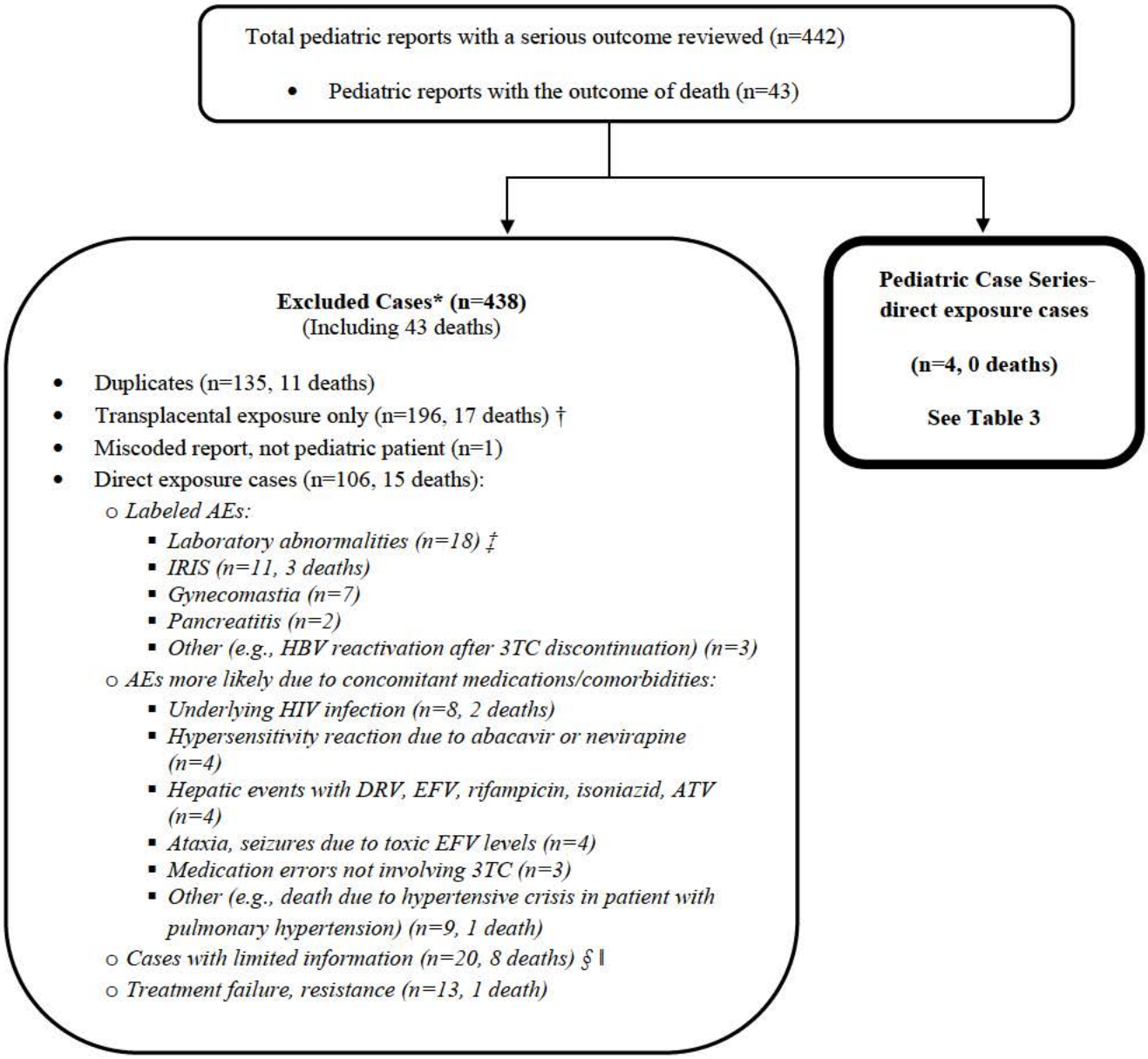
Disproportionality analyses using Empirica Signal found that the adverse events with the highest EB05 scores for the pediatric age group were either disease-related (such as *tuberculoma of central nervous system*), already labeled (such as *immune reconstitution inflammatory syndrome*), or related to transplacental exposure (such as *low birth-weight baby*).

DPV conducted a review of the adverse events *retinoblastoma*, *transplant dysfunction*, and *hemiplegia* because the EB05 score was elevated for the pediatric age group and not elevated for the adult age group, and the adverse events are unlabeled. The events were either due to concomitant medications (transplant complications from efavirenz-associated hepatic failure), underlying disease (hemiplegia due to HIV encephalopathy), complications of labeled events (hemiplegia due to central nervous system (CNS) tuberculosis-associated IRIS or varicella zoster IRIS), or related to transplacental exposure (literature report evaluating pediatric cancer rates in patients with transplacental exposure to antiretroviral therapy). No new safety signals were identified using disproportionality analyses.

3.3 SELECTION OF SERIOUS PEDIATRIC CASES IN FAERS

We retrieved 442 pediatric reports with a serious outcome (See Table 2). See **Figure 1.** below for the selection of cases to be summarized in **Sections 3.4 and 3.6.**

Figure 1 Selection of Serious Pediatric Cases with Lamivudine



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

† Transplacental exposure deaths-Sixteen of the 17 cases were reported in conjunction with prematurity, fetal growth restriction, small for dates babies, or genetic defects. One case reported sudden infant death syndrome (SIDS) in a 3-month-old infant whose mother was treated during pregnancy with lamivudine for HBV.

‡ Laboratory abnormalities-Sixteen of the 18 cases of laboratory abnormalities (such as anemia, neutropenia) were reported in neonates and infants treated with lamivudine plus zidovudine (8) or lamivudine plus stavudine (8) for prevention of mother to child transmission (PMTCT) of HIV. The event of hypertriglyceridemia, which was generally mild and transient, was also reported in 7 cases.

§ Fatal cases with limited information - Eight cases with fatal outcome and limited information (such as unknown cause of death, clinical course) were reported. Seven were from an observational study literature report that evaluated the durability and effectiveness of non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based antiretroviral therapy in perinatally HIV-infected, treatment-naïve adolescents in Asia. In addition to lamivudine, all seven patients were treated with concomitant nevirapine plus zidovudine or stavudine. CD4 counts reported were generally low (<200 cells/mm3).

‖ Non-fatal cases with limited information - Six were French cases of neurologic events (including neuroimaging abnormalities, psychomotor and cognitive delay associated with mitochondrial dysfunction) in HIV-negative pediatric patients born prior to 2000 in association with transplacental exposure to NRTIs, including didanosine, stavudine, zidovudine, and lamivudine. The patients were treated postnatally with zidovudine and lamivudine for PMTCT of HIV. The most recent U.S. HIV Treatment Guidelines state that evidence for clinically apparent effects of mitochondrial toxicity are conflicting and do not permit definitive conclusions about whether perinatal exposure to NRTIs might affect the long-term risk of organ system toxicities in children. [2]

Abbreviations: AE, adverse event; IRIS, immune reconstitution inflammatory disease; HBV, hepatitis B virus; 3TC, lamivudine; DRV, darunavir; ATV, atazanavir; EFV, efavirenz

3.4 CHARACTERISTICS OF PEDIATRIC CASE SERIES

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3 Characteristics of Pediatric Case Series with Lamivudine Received in FAERS between March 23, 2015 and January 11, 2018 (N=4)

Age	2 days	1
	2 weeks	1
	7 years	1
	12 years	1
Sex	Male	1
	Female	3
Country	Foreign	4
Reported Reason for Use	PMTCT of HIV	2
	HIV nPEP	1
	Not reported	1
Type of exposure	Direct exposure	2
	Direct + transplacental	2
Serious Outcome*	Hospitalized	3
	Congenital anomaly	1
	Other serious	1

Table 3 Characteristics of Pediatric Case Series with Lamivudine Received in FAERS between March 23, 2015 and January 11, 2018 (N=4)

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

PMTCT = Prevention of mother-to-child transmission
nPEP = non-occupational post-exposure prophylaxis

3.5 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

3.6 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

Of the four non-fatal cases in pediatric patients included in our case series, there were no new safety signals identified. See Appendix D for complete summaries and comments for each of these cases.

3.6.1 Unlabeled events: Gastroduodenal ulcer (1), gastrointestinal hemorrhage (1)

One case (FAERS #12787764) reported gastroduodenal ulcer with bleeding in a 7-year-old female with a temporal relationship to lamivudine and zidovudine use for non-occupational post-exposure prophylaxis.

Reviewer Comments: We explored gastrointestinal ulcer as an adverse event of interest for lamivudine in all age groups. We searched the FAERS database for reports of lamivudine and the adverse event terms gastric ulcer haemorrhage, gastrointestinal ulcer, gastroduodenal ulcer, gastric ulcer, and gastrointestinal ulcer haemorrhage. The search retrieved 28 foreign cases in adults in association with lamivudine since approval. No additional compelling cases were identified. The cases reported confounding factors (such as concomitant non-steroidal anti-inflammatory drugs, history of alcoholism) or contained insufficient information to assess causality.

3.6.2 Unlabeled events: Product size issue (1), oropharyngeal pain (1), dysphagia (1)

One case (FAERS #13790314) reported mucosal inflammation, dysphagia, oropharyngeal pain, and product size issue in a 12-year-old female six months after beginning Triumeq® (a fixed dose combination drug containing lamivudine, abacavir, dolutegravir) for an unknown indication. Concomitant medication included methotrexate for an unknown indication.

Reviewer Comments: The product size issue was likely due to the symptoms of dysphagia and mucositis. Stomatitis is labeled for lamivudine and methotrexate, and mucositis is a known adverse event for many chemotherapy drugs, including methotrexate. A more definitive causal assessment is not possible without additional details (such as methotrexate indication, dosing, route, regimen, and therapy dates).

3.6.3 Unlabeled event: Thrombocythemia (1)

One case (FAERS #3794767) reported hepatomegaly and thrombocythemia in a female neonate. At birth, stavudine syrup and lamivudine syrup therapies were initiated for five weeks for PMTCT of HIV. At two weeks of age, the patient experienced hepatomegaly. On day of life 15, the patient experienced thrombocythemia; platelet count was 933,000 (units not reported). Thrombocythemia was present at three months of age; platelet count was 539,000. Hepatomegaly was present at four months of age. The patient had a normal clinical and neurological assessment at 9 months and 24 months of age, and no biological disorders were noted.

Reviewer Comments: Thrombocythemia is an unlabeled adverse event for lamivudine. Hepatomegaly is labeled. There is a temporal association between onset of events and lamivudine use, however, the case offers no detailed reporting of laboratory values and physical findings to reasonably rule out other etiologies (such as essential thrombocytosis).

3.6.4 Unlabeled event: Gastroduodenitis (1)

One case (FAERS #3768872) reported green emesis, abdominal distention, hepatomegaly, increased liver function tests, polypnea, and punctiform exanthema on the thorax in a 2-day-old male one day after beginning zidovudine and lamivudine syrup for PMTCT of HIV. Lamivudine was discontinued after day of life 2 due to the events. An upper gastrointestinal endoscopy procedure at day of life 3 revealed severe gastroduodenitis. The patient received simethicone, oxide aluminum, ranitidine, and domperidone. The patient clinically improved on day of life 4 after 24 hours of bowel rest. The outcome is unknown.

Reviewer Comments: Gastroduodenitis is an unlabeled adverse event for lamivudine. Hepatomegaly, vomiting, increased liver function tests, and rash are labeled. The digestive events were reported with a temporal relationship to lamivudine use and abated following lamivudine discontinuation (positive dechallenge). It is possible the baby had intolerance to lamivudine syrup. Plausible alternative etiologies include protein intolerance and symptomatic delayed gastric emptying. A more definitive causal assessment is not possible without additional information regarding clinical course, and further details from the patient's clinical workup.

4 DISCUSSION

Of the pediatric FAERS reports reviewed, there were no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly attributable to lamivudine. No concerning use outside the approved indications was identified. Use of lamivudine was mainly for treatment of HIV infection and PMTCT of HIV.

Although we reviewed all serious FAERS reports in pediatric patients received from 23-Mar-2015 (pediatric labeling date) to 11-Jan-2018, only four non-fatal cases were included in our case series. Most reports described adverse events that were attributable to concomitant medications or comorbidities (such as efavirenz-related hepatotoxicity, ataxia or seizure, abacavir or nevirapine related hypersensitivity reactions, medication errors not involving lamivudine), were consistent with labeled events (such as IRIS, gynecomastia, pancreatitis, hepatitis B reactivation following lamivudine discontinuation), or contained insufficient information to assess causality (such as cases with no reported cause of death). Only a small number (four of the 110 direct exposure reports) were U.S. cases.

The four non-fatal cases included in our case series described unlabeled adverse events (gastroduodenal ulcer/bleeding in a 7-year-old female-1, product size issue/oropharyngeal pain/dysphagia in a 12-year-old female-1, thrombocythemia in a neonate -1, and gastroduodenitis in a neonate-1). The cases had alternative plausible explanations to account for the adverse events (such as dysphagia due to methotrexate-associated mucositis), or had limited case details which precluded a meaningful causality assessment. Further exploration of gastrointestinal ulcer as an adverse event of interest for lamivudine in all age groups in FAERS did not yield additional compelling cases

Of the four non-fatal cases in our case series, two reported use of lamivudine for PMTCT of HIV, and one reported use of lamivudine for nPEP. Although these are not approved indications, use of lamivudine for PMTCT of HIV infection is included in the U.S. HIV Treatment Guidelines and use of lamivudine for nPEP is included in the CDC guidelines for post-exposure prophylaxis. [3 4]

No new safety signals were identified with disproportionality analysis of all lamivudine pediatric and adult FAERS reports since approval.

5 CONCLUSION

DPV did not identify any pediatric safety concerns with lamivudine at this time.

6 RECOMMENDATIONS

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

7 REFERENCES

1. Epivir {package insert]. Research Triangle Park, NC: ViiV Healthcare; revised April 2018.

2. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed March 3, 2018, section E-39-43.

3. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed March 3, 2018, section E-6-20.

4. Centers for Disease Control and Prevention Updated Guidelines for Antiretroviral Postexposure Prophylaxis after Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV-United States, 2016. Available at https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf. Accessed March 3, 2018, section VII-C, pp 30-32.

5. Kucine N, Chastain KM, Mahler MB, Bussel JB. Primary Thrombocytosis in Children. Haematologica. 2014; 99:620-628.

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 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. DATA MINING OF FAERS USING EMPIRICA SIGNAL

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.3 APPENDIX C. LINE LISTING OF THE FAERS CASE SERIES FOR LAMIVUDINE (N=4)

Ref #	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer #	Case Type	Age	Sex	Country Derived	Serious Outcome *
1	28-Sep-2016	12787764 13050328 (dup) 12789663 (dup)	2 1 2	FR-GLAXOSMITHKLINE-FR2016GSK140162 FR-ABBVIE-16P-056-1813483-00 FR-VIIV HEALTHCARE LIMITED-FR2016GSK140162	Expedited (15-Day)	7 years	Female	FRA	HO
2	25-Jul-2017	13790314 14327138 (dup) 13976397 (dup) 13947155 (dup) 13932481 (dup) 13928087 (dup) 13922331 (dup) 13916952 (dup) 13904992 (dup)	6 1 4 4 1 1 4 3 2	GB-VIIV HEALTHCARE LIMITED-IE2017GSK114719 PHHY2017IE194325 IE-ORION CORPORATION ORION PHARMA-TREX2017-2608 GB-TEVA-801861ACC GB-ACCORD-057863 PHFR2017IE007072 PHFR2017IE007004 GB-PFIZER INC-2017368242 GB-ORION CORPORATION ORION PHARMA-TREX2017-2608	Expedited (15-Day)	12 years	Female	IRL	HO
3	29-May-2002	3794767 11907993 (dup)	1 1	US-BRISTOL-MYERS SQUIBB COMPANY-11867892 FR-BRISTOL-MYERS SQUIBB COMPANY-11867892	Expedited (15-Day)	14 days	Female	FRA	OT
4	8-Mar-2002	3768872 11906150 (dup)	1 2	FR-BRISTOL-MYERS SQUIBB COMPANY-11742418 US-BRISTOL-MYERS SQUIBB COMPANY-11742418	Expedited (15-Day)	2 days	Male	FRA	CA, 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, or a congenital anomaly/birth defect, required intervention and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. A report may have more than one serious outcome.

Abbreviations: Dup, Duplicate report for same patient; HO, Hospitalization; OT, Other medically significant, CA, Congenital Anomaly

8.4 APPENDIX D. FAERS CASE SUMMARIES FOR THE PEDIATRIC CASE SERIES WITH LAMIVUDINE (N=4)

FAERS Case Number 12787764 (duplicate reports: 12789663, 13050328)

Initial FDA Received Date: 28-Sep-2016

Country: France

Unlabeled events: Gastroduodenal ulcer (1), gastrointestinal hemorrhage (1):

A 7-year-old female patient developed a gastroduodenal ulcer after beginning HIV non-occupational exposure prophylaxis (nPEP) with lamivudine, zidovudine, and lopinavir + ritonavir following an accidental needle stick from a used needle in the street. The patient also received hepatitis B immunization. Two days after beginning prophylaxis, lopinavir + ritonavir was discontinued due to diarrhea. The patient experienced persistent abdominal pain during lamivudine and zidovudine use. One month after beginning prophylaxis she had onset of diarrhea (10 stools daily) with worsening of abdominal pain. Lamivudine and zidovudine were discontinued. She was diagnosed with viral gastroenteritis and was treated with Adiaril (electrolyte solution) and paracetamol. Her stool frequency decreased to 4 per day and her abdominal pain partially improved. One week later the patient's mother observed black stools and took the patient to the emergency room. Hydrogen peroxide test was positive and the patient was hospitalized. She had no fever and her blood pressure was 98/62. Clostridium test was negative, C-reactive protein was 6.6 mg/L (normal < 5 mg/L), Hemoglobin 11.5 g/dL, neutrophil count 2100/mm3, platelet count 369,000/L, creatinine 46 mcmol/L, potassium 4 mmol/L, sodium 140 mmol/L. Stool analysis was negative. She was treated with Spasfon (phloroglucinol). During hospitalization, melena did not recur and her hemoglobin was stable at 10.9 g/dl. Diarrhea and abdominal pain improved and patient was discharged 3 days later. The following month she had negative results for HIV, hepatitis B surface antigens, and hepatitis C virus serology.

Reviewers' comments: Gastroduodenal ulcer and bleeding are unlabeled adverse events for lamivudine. Diarrhea and abdominal pain are labeled for both lamivudine and zidovudine. The temporal relationship suggests a possible causal relationship to lamivudine and zidovudine use. Exacerbation of ulcer by viral gastroenteritis infection or other stressors is a plausible mechanism for upper gastrointestinal bleed and melena. A more definitive causal assessment is not possible without additional information regarding the patient's baseline health, past medical history, exposures, concomitant medications, and additional diagnostic tests (such as endoscopy). A FAERS database search (see section 3.6.1) in all age groups did not identify additional compelling cases of gastrointestinal ulcer in association with lamivudine since approval. Although nPEP is not an approved indication, use of lamivudine for nPEP is included in the 2016 Center for Disease Control (CDC) updated guidelines for nPEP. [4]

FAERS Case Number 13790314 (duplicate reports: 13904992, 13916952, 13922331, 13928087, 13932481, 13947155, 13976397, 14327138)

Initial FDA Received Date: 25-Jul-2017

Country: Ireland

Unlabeled events: Product size issue (1), oropharyngeal pain (1), dysphagia (1):

A 12-year-old female patient received Triumeq® (lamivudine, abacavir, dolutegravir) for an unknown indication from an unknown start date. The patient received methotrexate for the treatment of an unknown indication (possibly lymphoma) from an unknown start date at an unknown dose and frequency (route unknown). Six months after beginning Triumeq, the patient developed mucosal inflammation, oropharyngeal pain and dysphagia. The patient was hospitalized for these events. The patient had difficulty swallowing and complained about the size of Triumeq pill.

Reviewers' comments: Product size issue, oropharyngeal pain, and dysphagia are unlabeled adverse events for lamivudine. Stomatitis is labeled for lamivudine and methotrexate and mucositis is a known adverse event for many chemotherapy drugs, including methotrexate. A more definitive causal assessment is not possible without additional details (such as methotrexate dosing, route, regimen, and therapy dates). The product size issue was likely related to the symptoms of dysphagia and mucositis and furthermore, the size issue was not due to lamivudine (Epivir), but was due to the size of Triumeq®, a fixed dose combination drug containing abacavir, lamivudine and dolutegravir. Although lamivudine indication was not explicitly stated, it can be inferred that indication was treatment of HIV infection due to combination antiretroviral therapy and duration of therapy.

FAERS Case Number 3794767 (duplicate report: 11907993, resubmitted in 2016)

Initial FDA Received Date: 29-May-2002

Country: France

Unlabeled event: Thrombocythemia (1): A case report was received via the Antiretroviral Pregnancy Registry. An HIV-infected mother received stavudine, lamivudine, nelfinavir, interferon, and methadone during pregnancy. Nelfinavir therapy was interrupted from week 7 to week 18 of gestation. The mother received intravenous zidovudine during delivery via Cesarean section. At birth, the female newborn patient weighed 2,940 grams, measured 49 cm in length and 34 cm in head circumference, and had an Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score was 9/10. Subsequently, stavudine syrup and lamivudine syrup therapies were initiated for five weeks for PMTCT of HIV. At two weeks of age, the patient experienced hepatomegaly. On day of life 15, the patient experienced thrombocythemia; platelet count was 933,000 (units not reported). Thrombocythemia was present at three months of age; platelet count was 539,000. Hepatomegaly was present at four months of age. The patient had a normal clinical and neurological assessment at 9 months and 24 months of age. No biological disorders were noted.

Reviewers' comments: Thrombocythemia is an unlabeled adverse event for lamivudine. Hepatomegaly is labeled. There is some temporal association between onset of events and lamivudine use, however, the case offers no detailed reporting of laboratory values and physical findings to reasonably rule out other etiologies for the patient's findings. Other plausible

alternative causes for the patient's findings include essential thrombocytosis, other myeloproliferative and inflammatory conditions, and transient reactive (secondary) thrombocytosis.[5] Although not an approved indication, use of lamivudine in combination with other antiretrovirals for PMTCT of HIV infection is included in U.S. HIV Treatment Guidelines.[3]

FAERS Case Number 3768872 (duplicate report: 11906150, resubmitted in 2016)

Initial FDA Received Date: 8-Mar-2002

Country: France

Unlabeled event: Gastroduodenitis (1): An HIV-infected mother received didanosine, lamivudine and nevirapine during her entire pregnancy. She received, on an unspecified date, for an unspecified reason, during an unspecified time, amoxicillin, nicardipine, betamethasone, chlorquinaldol, promestriene and econazole. She experienced premature labor at the 31 weeks gestation following a fall and she had an emergency delivery at 39 weeks gestation due to abnormal fetal heart rate. She received zidovudine infusion during delivery. At birth, the male newborn patient weighed 3,990 grams, measured 53cm in length and 36cm in head circumference, and had an APGAR score of 10/10. The patient was born with a ventricular septal defect. The patient began zidovudine and lamivudine syrup for PMTCT of HIV. On day of life 2, the patient experienced regurgitation, abdominal distention, green emesis, hepatomegaly, polypnea, and punctiform exanthema on the thorax. Lamivudine therapy was suspended after day of life 2 due to the patient's symptoms. The baby experienced aspartate transaminase (AST) increased (values not reported) at day 0, 2, 3, 4; alanine transaminase (ALT) increased (values not reported) at day 2, 3, 4; lactic dehydrogenase (LDH) increased (value not reported) at day 4. C reactive protein: < 5 (units not reported) at day 2. An upper gastrointestinal endoscopy procedure at day of life 3 revealed severe gastroduodenitis. The patient received simethicone, oxide aluminum, ranitidine, and domperidone. The patient clinically improved on day of life 4 after 24 hours of bowel rest. The outcome is unknown.

Reviewers' comments: Gastroduodenitis is an unlabeled adverse event for lamivudine. Hepatomegaly, vomiting, increased liver function tests, and rash are labeled. The digestive events were reported with a temporal relationship to lamivudine use and abated following lamivudine discontinuation (positive dechallenge). It is possible the baby had intolerance to lamivudine syrup. Plausible alternative etiologies include protein intolerance and symptomatic delayed gastric emptying. A more definitive causal assessment is not possible without additional information regarding clinical course, and further details from the patient's clinical workup. Although not an approved indication, use of lamivudine in combination with other antiretrovirals for PMTCT of HIV infection is included in the U.S. HIV Treatment Guidelines.[3]

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/s/

PAULA L GISH
05/22/2018

IVONE E KIM
05/22/2018

KELLY Y CAO
05/22/2018

IDA-LINA DIAK
05/22/2018