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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Names:	Symfi Lo™ (efavirenz 400mg + lamivudine 300mg + tenofovir disoproxil fumarate 300mg) Symfi™ (efavirenz 600mg + lamivudine 300mg + tenofovir disoproxil fumarate 300mg)
Pediatric Labeling Approval Date:	Symfi Lo™ 05-Feb-2018 Symfi™ 22-Mar-2018
Application Type/Number:	Symfi Lo™ NDA 208255 Symfi™ NDA 022142
Applicant/Sponsor:	Mylan
OSE RCM #:	2019-2032

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symfi Lo™ and Symfi™ in pediatric patients through age 17 years. 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 serious unlabeled adverse events associated with Symfi Lo and Symfi in pediatric patients.

The FDA approved Symfi Lo on 05-Feb-2018 and Symfi on 22-Mar-2018. Both Symfi Lo and Symfi are a three-drug combination of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleo(t)side reverse transcriptase inhibitors. Symfi Lo and Symfi each contain 300mg 3TC and 300mg TDF, but Symfi Lo contains a lower dose of EFV than Symfi (400mg versus 600mg).

Symfi Lo is approved as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg. Symfi is approved as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 40 kg. This PREA review was triggered by pediatric labeling that Symfi Lo and Symfi received at initial approval.

DPV reviewed all FAERS reports with Symfi Lo and Symfi use received by FDA from 05-Feb-2018 to 30-Sep-2019 and did not find any pediatric reports suggesting a new safety signal.

In summary, Symfi Lo and Symfi are approved for use in the pediatric population in patients weighing at least 35 kg and 40 kg, respectively. DPV did not identify any new pediatric safety concerns for Symfi Lo and Symfi based on the FAERS data alone. DPV recommends no regulatory action for Symfi Lo or Symfi specific to pediatric patients at this time and will continue to monitor adverse events associated with their use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symfi Lo™ and Symfi™ in pediatric patients through age 17 years. 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 serious unlabeled adverse events associated with Symfi Lo and Symfi in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Both Symfi Lo and Symfi are a three-drug fixed-dose combination tablet of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleo(t)side reverse transcriptase inhibitors. Symfi Lo and Symfi each contain 300mg 3TC and 300mg TDF but Symfi Lo offers a lower dose of EFV than Symfi (400mg versus 600mg) for patients weighing less than 40 kg.

The FDA approved Symfi Lo (EFV 400mg +3TC 300mg +TDF 300mg) on 05-Feb-2018 as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg. Symfi (EFV 600mg + 3TC 300mg + TDF 300mg) was approved on 22-Mar-2018 as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 40 kg. This PREA review was triggered by pediatric labeling that Symfi Lo and Symfi received at initial approval.

The safety and effectiveness of Symfi Lo in pediatric patients weighing at least 35 kg and the safety and effectiveness of Symfi in pediatric patients weighing at least 40 kg was established based on clinical studies using the individual components (EFV, 3TC, and TDF), which are currently approved for use in the pediatric population. A comprehensive overview of available safety data is included below, including adult clinical trial data for Symfi and Symfi Lo, and pediatric safety data from clinical trials of the individual components (EFV, 3TC, and TDF).

1.1.1 Adult Clinical Trial Data

The safety and efficacy of Symfi Lo and Symfi in the treatment of HIV-1 infection in adults was established in two double-blind, randomized, multinational clinical trials in antiretroviral-naïve adults[1]; no pediatric patients were enrolled in Trial 903 or ENCORE1:

- Trial 903, which evaluated the efficacy of the three-drug regimen EFV 600mg + 3TC 300mg + TDF 300mg (N=299, hereafter referred to as 'TDF group') compared to EFV 600mg + 3TC 300mg + stavudine (d4T) 40mg (N=301, hereafter referred to as 'd4T group')
- Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy (ENCORE1), which evaluated the comparability of a 400mg dose of EFV in a triple drug regimen (N=321) to a 600mg dose of EFV in a triple drug regimen (N=309)

Trial 903

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms and included dizziness, diarrhea, and nausea. Rash (Grades 2-4) occurred in 18% of subjects in the

TDF group compared to 12% of subjects in the d4T group. Fasting cholesterol and fasting triglyceride elevations were more common in the d4T group compared with the TDF group. There was a significantly greater mean percentage decrease from baseline in bone mineral density (BMD) at the lumbar spine in subjects in the TDF group (-2.2% ± 3.9) relative to subjects in the d4T group (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF group vs. -2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated subjects vs. 21% of the d4T-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in four subjects in the TDF group and six subjects in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range.

The ENCORE1 trial

At Week 48, 40% of EFV 400mg recipients and 48% of EFV 600mg recipients reported central nervous system disorders. The most common symptoms (> 10%) for EFV 400mg recipients and EFV 600mg, respectively, were dizziness (27% vs. 35%) and headache (11% vs. 11%). The frequency (regardless of causality) of the most common (occurring in >1% patients) psychiatric events among patients who received EFV 400mg or EFV 600mg regimens, respectively, were: abnormal dreams (8.7%, 11.3%), insomnia (6.2%, 6.5%), somnolence (3.1%, 3.9%), depression (3.1%, 1.6%), nightmare (1.9%, 2.6%), sleep disorder (2.2%, 1.3%), and anxiety (1.2%, 1.3%).

1.1.2 Pediatric Clinical Trial Data

The pediatric indications and clinical studies used to gain pediatric labeling for each component are described below:

- EFV (Sustiva®) was initially approved in 1998 and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kg. The daily EFV dose in pediatric patients weighing 32.5 kg to less than 40 kg is 400mg, and aligns with the daily dose for Symfi Lo, which is approved in pediatric patients weighing at least 35 kg. The daily EFV dose in pediatric patients weighing at least 40 kg is 600mg, and aligns with the daily dose for Symfi, which is approved in pediatric patients weighing at least 40 kg. [2]

  The safety, pharmacokinetic profile, and virologic and immunologic responses of EFV were evaluated in antiretroviral-naïve and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three open-label clinical trials. Assessment of adverse reactions was based on the three clinical trials in 182 HIV-1 infected pediatric patients who received EFV in combination with other antiretroviral agents for a median of 123 weeks. The adverse reactions observed in the three trials were similar to those observed in clinical trials in adults, except that rash was more common in pediatric patients, with a higher frequency of Grade 3 or 4 rash as compared to adults.

- 3TC (Epivir®) was initially approved in 1995 and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection adults and pediatric patients 3 months of age and older. The daily dose for 3TC in pediatric patients weighing ≥ 25 kg is 300mg, and aligns with the daily dose in both Symfi and Symfi Lo. [3]

  Initially the safety and efficacy of 3TC in pediatric patients was evaluated using twice-daily dosing in a multicenter, randomized, double-blind trial (ACTG300) that compared 3TC plus zidovudine to 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 3TC plus zidovudine. Selected clinical adverse reactions and physical findings (greater than or equal to 5% frequency) in 3TC 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/mm^3, hemoglobin < 7.9 g/dL, platelets < 50,000/mm^3, 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 was fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects in open-label trials (NUCA2002 and NUCA2005) receiving 3TC alone or in combination with other antiretroviral agents. Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in NUCA2002, 6 subjects (9%) in NUCA2005, and 2 subjects (less than 1%) in ACTG300.

  Once-daily dosing in pediatric patients was evaluated in a 5-year randomized, multicenter trial (ARROW trial, COL105677), which compared the safety and efficacy of once-daily dosing with twice-daily dosing of 3TC and abacavir, in combination with a third antiretroviral drug in HIV-1 infected treatment-naïve subjects aged 3 months to 17 years (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.

- TDF (Viread®) was initially approved in 2001 and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older weighing at least 10 kg. TDF is also approved for the treatment of chronic hepatitis B in adults and pediatric patients 2 years and older weighing at least 10 kg. The daily dose for TDF in pediatric patients weighing > 35 kg is 300mg, and is aligned with the dose in Symfi Lo and Symfi. [4]

  Assessment of adverse reactions was based on two randomized trials (Trials 352 and 321) in 184 HIV-1 infected pediatric subjects (2 years to less than 18 years of age) who received treatment with TDF (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials in adults. In Trial 352, 89 pediatric subjects (2 years to less than 12 years of age) received TDF for a median exposure of 104 weeks. Of these,

four subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these four subjects presented with hypophosphatemia plus decreases in total body or spine BMD Z-score.

In clinical trials in pediatric and adolescent HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and were suggestive of increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in TDF-treated chronic hepatitis B virus (HBV) infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials for TDF use for HBV and HIV, skeletal growth (height) appeared to be unaffected. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are currently unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children, is also unknown.

OSE has not previously presented a Symfi Lo or Symfi pediatric evaluation to the Pediatric Advisory Committee (PAC). However, OSE has previously conducted pediatric evaluations for each of the individual components. The past OSE reviews for the PAC are summarized below in Table 1.

Table 1. Past OSE reviews evaluating individual drug components of Symfi Lo and Symfi in the pediatric population for the PAC

Drug component	Pediatric labeling change date and product	Date of OSE review	Date and type of presentation	PAC recommendations
EFV	02-May-2013 Sustiva (EFV)	08-Aug-2016	14-Sep-2016 Meeting	PAC concurred with FDA proposal to add the term catatonia to labeling, continue post-marketing safety surveillance
3TC	17-Sep-2015 Epzicom (ABC+3TC) 23-Mar-2015 Epivir (3TC)	11-Jul-2018 22-May-2018	12-Sep-2018 Web 13-Jun-2018 Web	Continue post-marketing safety surveillance Continue post-marketing safety surveillance
TDF	27-Jan-2017 Stribild (EVG+COBI+FTC+TDF)	30-May-2019	23-Sep-2019 Web	Continue post-marketing safety surveillance
	16-Aug-2012 Viread (TDF)	22-Jul-2014	23-Sep-2014 Meeting	Continue post-marketing safety surveillance
	18-Jan-2012 Viread (TDF)	06-Nov-2013	21-Apr-2014 Meeting	Continue post-marketing safety surveillance
	08-Jul-2011 Truvada (TDF+FTC)	02-Feb-2017	03-Feb-2017 Web	Continue post-marketing safety surveillance

	24-Mar-2010 Viread (TDF)	12-Mar-2012	07-May-2012 Meeting	Continue post-marketing safety surveillance
Abbreviations: PAC=Pediatric Advisory Committee, W/P = WARNINGS and PRECAUTIONS, EFV=efavirenz, 3TC=lamivudine, ABC=abacavir, TDF=tenofovir disoproxil fumarate, EVG=elvitegravir, COBI=cobicistat, FTC=emtricitabine				

1.2 RELEVANT LABELED SAFETY INFORMATION

Symfi Lo and Symfi labeling are similar and provide the following safety information (excerpted from the pertinent sections). For further Symfi and Symfi Lo labeling information, please refer to full prescribing information for each. [5 6]

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.1)**

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

- Patients with previous hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of these products. (4)
- Coadministration with elbasvir/grazoprevir. (4)

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.2)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering with concurrent or recent use of nephrotoxic drugs. (5.4)
- Serious Psychiatric Symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.5)
- Nervous System Symptoms (NSS): NSS are frequent, usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.6)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.8)

- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.9, 8.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of SYMFI LO and SYMFI, should be used with caution. Treatment with SYMFI LO and SYMFI should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur. (5.10)
- Convulsions: Use caution in patients with a history of seizures. (5.11)
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.12)
- Decreases in Bone Mineral Density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.13)
- Immune Reconstitution Syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.14)
- Redistribution/Accumulation of Body Fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.15)

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

- SYMFI LO: Most common adverse reactions (> 5% with SYMFI LO) are rash and dizziness. (6)
- SYMFI: Most common adverse reactions with SYMFI are impaired concentration, abnormal dreams, headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, dizziness, insomnia, pain, depression, asthenia, and cough. (6)

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

- Should not be administered with other antiretroviral medications for the treatment of HIV-1 infection. (7.1)
- Coadministration of SYMFI LO or SYMFI can alter the concentrations of other drugs and other drugs may alter the concentration of SYMFI LO or SYMFI. The potential for drug-drug interactions should be considered before and during therapy. (5.3, 7)

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

- Pregnancy: Women should avoid pregnancy during EFV therapy, a component of SYMFI LO and SYMFI, and for 12 weeks after discontinuation. (5.7, 8.1, 8.3)
- Lactation: Breastfeeding not recommended due to potential for HIV transmission. (8.2)
- Females and Males of Reproductive Potential: Pregnancy testing and contraception are recommended. (8.3)

8.4 Pediatric Use:

SYMFI LO: The safety and effectiveness of SYMFI LO as a fixed-dose tablet in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on

clinical studies using the individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate).
SYMFI: The safety and effectiveness of SYMFI as a fixed-dose tablet in pediatric patients infected with HIV-1 and weighing at least 40 kg have been established based on clinical studies using the individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	02-Dec-2019
Time Period of Search	05-Feb-2018† - 30-Sep-2019
Search Type	Product-Manufacturer Reporting Summary
Product Terms	Product names: Symfi Lo, Symfi Product active ingredient: efavirenz\lamivudine\tenofovir disoproxil fumarate Product active moiety: efavirenz\lamivudine\tenofovir NDAs: 208255, 022142
MedDRA Search Terms (Version 22.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. Approval date for Symfi Lo	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from 05-Feb-2018 to 30-Sep-2019 with Symfi Lo and Symfi.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from 05-Feb-2018 to 30-Sep-2019 with Symfi Lo and Symfi			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	35 (3)	32 (0)	1 (0)
Pediatrics (0 - <17 years)	3 (0)	**3‡ (0)**	0 (0)
* 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.			

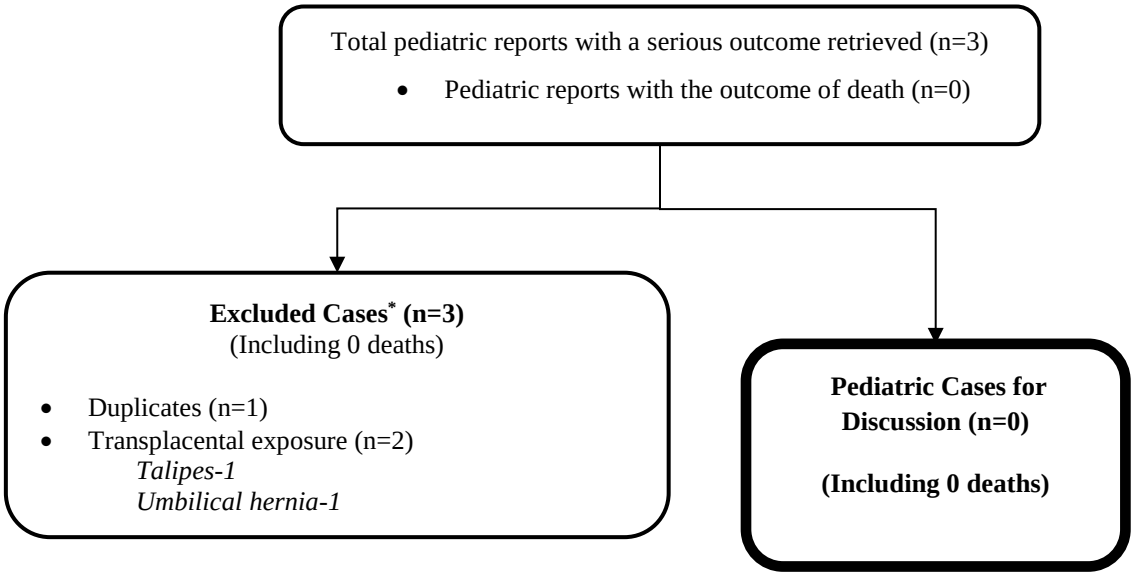
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved three serious pediatric reports from 05-Feb-2018 to 30-Sep-2019.

We reviewed and excluded all three FAERS pediatric reports. One of the three reports was a duplicate report. The two remaining cases (Preferred Terms: *Talipes* N=1, *Umbilical hernia* N=1) were transplacental exposure only and were excluded.

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

Figure 1. Selection of Serious Pediatric Cases with Symfi Lo and Symfi.



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

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=0)

We did not identify any non-fatal serious pediatric adverse event reports.

4 DISCUSSION

DPV reviewed all FAERS reports with Symfi Lo and Symfi use received by FDA from 05-Feb-2018 to 30-Sep-2019 and did not find any pediatric reports suggesting a new safety signal. No fatal adverse event reports were identified for pediatric patients. There were no new safety signals identified and no increase in the severity or frequency of any labeled adverse events specific to pediatric patients.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Symfi Lo and Symfi at this time based on the FAERS data alone.

6 RECOMMENDATION

DPV recommends no regulatory action for Symfi Lo or Symfi specific to pediatric patients at this time and will continue to monitor all adverse events associated with their use.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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