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:	February 1, 2019
Safety Evaluator:	Sarah Kang, Pharm.D., MSP, BCPS Division of Pharmacovigilance II (DPV II)
Medical Officer:	Ivone Kim, MD, FAAP DPV I
Team Leader:	Neha Gada, Pharm.D., BCPS DPV II
Deputy Division Director:	Ida-Lina Diak, Pharm.D., MS DPV II
Product Name:	Lyrica (pregabalin)
Pediatric Labeling Approval Date:	December 22, 2016
Application Type/Number:	NDA 21446, 21723, 21724, 22488
Applicant/Sponsor:	PF PRISM CV
OSE RCM #:	2018-1669

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for pregabalin in pediatric patients through age 16 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 pregabalin in pediatric patients.

The FDA initially approved Lyrica on December 30, 2004 for neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia in adults and subsequently approved it for fibromyalgia and neuropathic pain associated with spinal cord injury. The approved pediatric labeling is for fibromyalgia and adjunctive therapy for the treatment of partial onset seizures (POS) in patients 4 years of age and older. The fibromyalgia pediatric labeling change on December 22, 2016 under PREA triggered this current safety review. Lyrica was studied for fibromyalgia in the pediatric population but did not reach statistical significance and therefore did not gain FDA approval for the fibromyalgia indication in pediatric patients. The only FDA approved indication in the pediatric population is for adjunctive therapy for the treatment of POS in patients 4 years of age and older which was approved on May 3, 2018. This approval will trigger a future pediatric focused safety review.

We reviewed serious FAERS reports with pregabalin in the U.S. pediatric population (ages 0 to < 17 years) during the period December 22, 2015 through July 31, 2018. We identified no new safety signals or an increased severity or frequency of any labeled adverse events with pregabalin. However, we identified one case of an unintentional exposure resulting in central nervous system (CNS) depression in a patient for whom pregabalin is not indicated; the event occurred in the context of multiple co-administered products with potential for CNS depression.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lyrica (pregabalin) in pediatric patients through age 16 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 pregabalin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Pregabalin is a gamma-aminobutyric acid analog. FDA first approved pregabalin capsules on December 30, 2004 for the following indications in adult patients: 1) neuropathic pain associated with diabetic peripheral neuropathy and 2) postherpetic neuralgia. Pregabalin is available in 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, and 300mg capsules. On January 4, 2010, FDA approved pregabalin oral solution of 20mg/ml.

FDA approved pregabalin for adjunctive therapy for the treatment of partial onset seizures (POS) in adult patients on June 10, 2005 and for fibromyalgia in adult patients on June 21, 2007. FDA approved pregabalin for the additional indication of neuropathic pain associated with spinal cord injury on June 20, 2012. The fibromyalgia and POS indication approvals triggered PREA, however, PREA requirements were waived for the spinal cord injury indication.

On December 22, 2016, the Sponsor for Lyrica (pregabalin), PF Prism CV, fulfilled the post marketing requirement (PMR), but did not gain approval for the fibromyalgia indication. FDA revised the Pediatric Use section of the labeling, incorporating the results of PMR study A0081180. This pediatric labeling change triggered this PREA review. Safety and efficacy data reflected in the pediatric labeling change for fibromyalgia are described below:[1]

- A 15-week, placebo-controlled trial was conducted with 107 pediatric patients with fibromyalgia, ages 12 through 17 years, at Lyrica total daily doses of 75-450 mg per day. The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11-point numeric rating scale) showed numerically greater improvement for the pregabalin-treated patients compared to placebo-treated patients, but did not reach statistical significance. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.

On May 3, 2018, the Lyrica Sponsor fulfilled the PMRs for the POS indication and gained approval for indication extension to include treatment of POS in pediatric patients 4 years to 16 years of age. FDA revised the Pediatric Use section of the labeling, incorporating the results of

the POS clinical trial (A0081041) and pediatric extrapolation with supportive clinical pharmacology pediatric pharmacokinetic data (A0081074).

- The safety and effectiveness of Lyrica as adjunctive treatment for POS in pediatric patients 4 to 16 years of age have been established in a 12-week, double-blind, placebo-controlled study. Patients treated with Lyrica 10 mg/kg/day had, on average, a 21.0% greater reduction in partial onset seizures than patients treated with placebo ($p = 0.0185$). Patients treated with Lyrica 2.5 mg/kg/day had, on average, a 10.5% greater reduction in partial onset seizures than patients treated with placebo, but the difference was not statistically significant ($p = 0.2577$). The most common adverse reactions (≥5%) with Lyrica in this study were somnolence, weight increased, and increased appetite.
- The use of Lyrica 2.5mg/kg/day in pediatric patients is further supported by evidence from adequate and well controlled studies in adults with POS and pharmacokinetic data from adult and pediatric patients.

Pregabalin has not been presented before the Pediatric Advisory Committee previously.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

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

- Known hypersensitivity to pregabalin or any of its components. (4)

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

- Angioedema (e.g., swelling of the throat, head and neck) can occur, and may be associated with life-threatening respiratory compromise requiring emergency treatment. Discontinue Lyrica immediately in these cases. (5.1)
- Hypersensitivity reactions (e.g., hives, dyspnea, and wheezing) can occur. Discontinue Lyrica immediately in these patients. (5.2)
- Increased seizure frequency or other adverse reactions may occur if Lyrica is rapidly discontinued. Withdraw Lyrica gradually over a minimum of 1 week. (5.3)
- Antiepileptic drugs, including Lyrica, increase the risk of suicidal thoughts or behavior. (5.4)
- Lyrica may cause peripheral edema. Exercise caution when co administering Lyrica and thiazolidinedione antidiabetic agents. (5.5)
- Lyrica may cause dizziness and somnolence and impair patients' ability to drive or operate machinery. (5.6)

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

Most common adverse reactions (greater than or equal to 5% and twice placebo) in adults are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormal (primarily difficulty with concentration/attention). (6.1)

Most common adverse reactions (greater than or equal to 5% and twice placebo) in pediatric patients for the treatment of partial onset seizures are increased weight and increased appetite. (6.1)

Section 8 USE IN SPECIFIC POPULATIONS, the *Pediatric Use* subsection includes the following information *(excerpted):*

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy, Postherpetic Neuralgia, and Neuropathic Pain Associated with Spinal Cord Injury

Safety and effectiveness in pediatric patients have not been established.

Fibromyalgia

Safety and effectiveness in pediatric patients have not been established.

Adjunctive Therapy for Partial Onset Seizures

(See aforementioned summary for safety and efficacy in patients 4-16)

Safety and effectiveness in patients less than 4 years of age have not been established.

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	August 1, 2018
Time Period of Search	December 22, 2015† - July 31, 2018
Search Type	Product-Manufacturer Reporting Summary, Quick Query
Product Terms	Product Active Ingredient: pregabalin
Other criteria	U.S. only, serious outcome
* See **Appendix A** for a description of the FAERS database. † One year prior to approval date of pediatric labeling	

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 December 22, 2015 through July 31, 2018 with pregabalin.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from December 22, 2015 through July 31, 2018 with Pregabalin

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	16,572 (11,899)	8,798 (4,205)	1,283 (514)
Pediatrics (0 - <17 years)	92 (15)	76 (8)	2 (1)

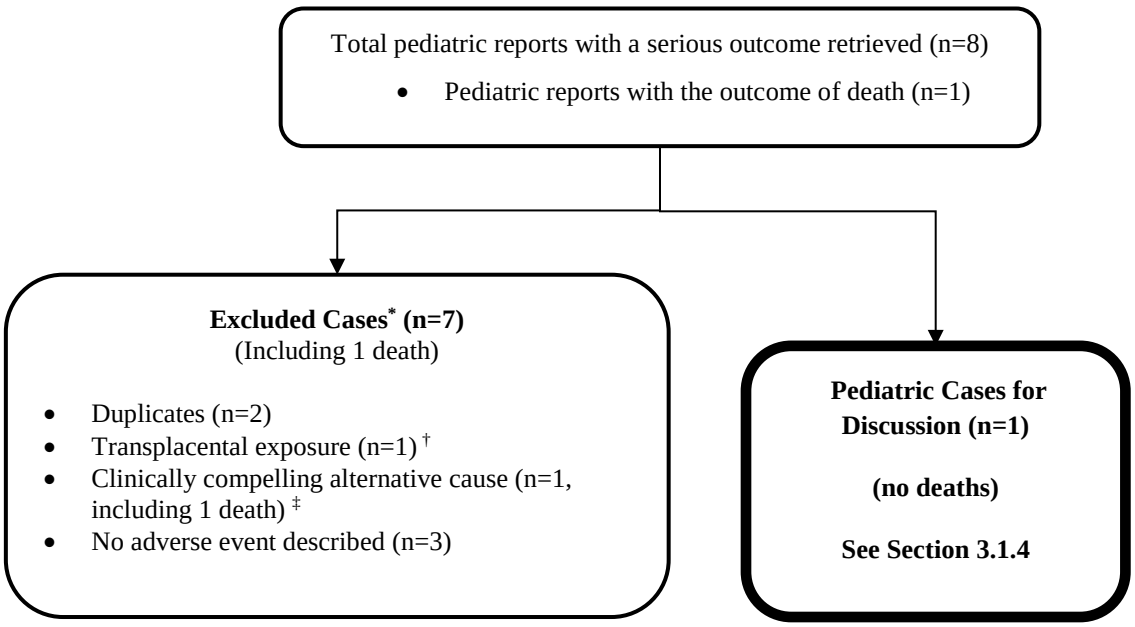
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved eight U.S. pediatric reports reporting a serious regulatory outcome from December 22, 2015 through July 31, 2018. We excluded seven reports from the case series after review. We summarize the remaining one case in the section 3.1.4 below. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Pregabalin



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

† One case reported transplacental exposure to multiple drugs including aripiprazole, citalopram hydrobromide, lansoprazole, hydromorphone hydrochloride, lorazepam, pregabalin and zolpidem. The neonate was born premature at 29 weeks gestation and experienced dyspnea requiring treatment in the neonatal intensive care unit.

The case lacked information to discern the extent to which each of the co-administered medications contributed to the events.

‡ One case described the patient's comorbid medical condition as a clinically compelling alternative cause for a fatal outcome. The case described a 15-year-old patient with a history of "failed initial multiagent chemotherapy, intensive relapsed leukemia chemotherapy, 2 cycles of blinatumomab and CAR T cell therapy" who received pregabalin for vincristine neuropathy. At an unknown date relative to pregabalin treatment, the patient developed sepsis and died. The patient's primary disease and myelosuppression following chemotherapy provide clinically compelling alternative mechanisms for the development of sepsis and death.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

3.1.4.1 Unintentional exposure

FAERS case #13940391, Version 1/ U.S./Expedited report:

A 2-year-old female rubbed her mother's compounded topical pain cream containing gabapentin (8%), pregabalin (2.5% w/v), clonidine (0.3%), and ketamine (10%) all over her face. The patient's mother promptly washed the patient's face with soap and water and took her to the emergency department. The patient was initially drowsy, however, shortly after ED arrival, she became apneic and was intubated. The patient did not experience bradycardia or hypotension. Within 24 hours from the time of exposure, she was extubated and discharged home. This case did not provide further information regarding treatments received during hospitalization.

Reviewer's comment:
This case represents an unintentional exposure to pregabalin, in addition to other medications, for an unapproved indication and age. The patient experienced central nervous system (CNS) and respiratory depression which are labeled events in gabapentin,[2] pregabalin,[1] clonidine[3] and ketamine[4] product labeling. The case lacks sufficient information to discern the extent to which any of the co-administered products may have contributed to the events.

4 DISCUSSION

We reviewed serious FAERS reports with pregabalin in the U.S. pediatric population (ages 0 to < 17 years) during the period December 22, 2015 through July 31, 2018. We identified one case of an unintentional exposure resulting in CNS depression in a patient for whom pregabalin is not indicated; the event occurred in the context of multiple unintentional co-administered products with potential for CNS depression. This singular case does not represent a new safety signal.

5 CONCLUSION

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

6 RECOMMENDATION

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

7 REFERENCES

1. Lyrica [Prescribing Information]. NY, NY: pfizer; May 2018.
2. Neurontin [Prescribing Information]. New York, NY: Pfizer; October 2017.
3. Catapres [Prescribing Information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; October 2011.
4. Ketamine Hydrochloride. *DailyMED*. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=58487c78-a641-4278-acc0-343596ee8683 Eatontown, NJ. West-Ward Pharmacueticals Corp; May 2017.

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=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	9/6/2017	13940391	1	US-PFIZER INC-2017378371	Expedited	2	F	U.S.	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, 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: HO=Hospitalization**

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IDA-LINA DIAK
02/01/2019 11:35:33 AM