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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 13, 2022
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Product Name:	Lyrica (pregabalin)
Pediatric Labeling Approval Date:	May 3, 2018; May 23, 2019
Application Type/Number:	NDA 021446 (capsule), NDA 021723 (capsule), NDA 021724 (capsule), NDA 022488 (solution)
Applicant:	Upjohn, Inc
TTT #:	2022-1379

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EXECUTIVE SUMMARY

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)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with pregabalin in pediatric patients.

The FDA approved pregabalin on December 30, 2004, for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia in adult patients. Since that time, pregabalin has received approval for new indications of 1) adjunctive therapy for the treatment of partial-onset seizures in adults, 2) fibromyalgia in adults, and 3) neuropathic pain associated with spinal cord injury in adults. The approved pediatric labeling is for the treatment of partial-onset seizures in pediatric patients 1 month of age and older. This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on May 3, 2018, and May 23, 2019.

We reviewed all FAERS U.S. serious cases with pregabalin in the pediatric population (ages 0 to <17 years) during the period of August 1, 2018, through September 12, 2022. Our evaluation did not identify any serious, unlabeled, non-fatal cases associated with pregabalin in the pediatric population. We did not identify any additional safety signals, increased severity or frequency of any labeled adverse events, or deaths directly associated with pregabalin.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for pregabalin in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV)-I conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA). This review focuses on U.S. 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.[1] On June 10, 2005, the FDA approved pregabalin for adjunctive therapy for the treatment of partial-onset seizures in adult patients.[2] Pregabalin subsequently received approvals from the FDA for the management of fibromyalgia and neuropathic pain associated with spinal cord injury in adults on June 21, 2007 and June 20, 2012, respectively. [2,3]

On December 22, 2016, the FDA approved the revision of the Pediatric Use section of the pregabalin labeling to incorporate the results of the postmarketing requirement (PMR) study to include "A 15-week, randomized, double-blind, parallel-group, placebo-controlled flexible-dose safety and efficacy study of pregabalin in adolescents (12 through 17 years old) with fibromyalgia."[4] The study did not demonstrate efficacy of pregabalin for the treatment of fibromyalgia in adolescent patients.

On May 3, 2018, the FDA approved the expanded use of pregabalin for the adjunctive therapy in the treatment of partial-onset seizures to include pediatric patients 4 years to 16 years of age based on a randomized, double-blind, placebo-controlled clinical trial in children 4-16 years of age with partial-onset seizures (Study A0081041) and on an extrapolation of efficacy from adult data with supportive clinical pharmacology pediatric pharmacokinetic data.[5,6]

On May 23, 2019, the FDA approved pregabalin for the expansion of the use of pregabalin for the adjunctive therapy in the treatment of partial-onset seizures to include pediatric patients 1 month to less than 4 years of age based on a randomized, double-blind, placebo-controlled pediatric clinical trial (Study A0081042).[7,8]

Lyrica (pregabalin) capsules and oral solution are currently indicated for the treatment of 1) neuropathic pain associated with diabetic peripheral neuropathy in adults; 2) postherpetic neuralgia in adults; 3) adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older; 4) fibromyalgia in adults; and 5) neuropathic pain associated with spinal cord injury in adults. Pregabalin is available in 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules, and 20 mg/ml oral solution.

DPV-II previously evaluated pediatric postmarketing adverse event reports with pregabalin in a review dated February 1, 2019,[9] which was prompted by the pediatric labeling change on

December 22, 2016. DPV-II's evaluation did not identify any new pediatric safety concerns, and recommended routine monitoring for adverse events with pregabalin. FDA presented their results to the Pediatric Advisory Committee (PAC) on March 28, 2019.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on May 3, 2018, and May 23, 2019.

1.2 RELEVANT LABELED SAFETY INFORMATION

A summary of the safety information from the HIGHLIGHTS OF PRESCRIBING INFORMATION section and Pediatric Use subsection of the pregabalin product labeling is reproduced below.[10]

---------- 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)
- Antiepileptic drugs, including LYRICA, increase the risk of suicidal thoughts or behavior. (5.3)
- Respiratory depression: May occur with LYRICA, when used with concomitant CNS depressants or in the setting of underlying respiratory impairment. Monitor patients and adjust dosage as appropriate. (5.4)
- LYRICA may cause dizziness and somnolence and impair patients' ability to drive or operate machinery. (5.5)
- Increased seizure frequency or other adverse reactions may occur if LYRICA is rapidly discontinued. Withdraw LYRICA gradually over a minimum of 1 week. (5.6)
- LYRICA may cause peripheral edema. Exercise caution when co-administering LYRICA and thiazolidinedione antidiabetic agents. (5.7)

----------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)

8 USE IN SPECIFIC POPULATIONS
8.4 *Pediatric Use*

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.

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.

Adjunctive Therapy for Partial-Onset Seizures
Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

4 to Less Than 17 Years of Age with Partial-Onset Seizures
The safety and effectiveness of LYRICA as adjunctive treatment for partial-onset seizures in pediatric patients 4 to less than 17 years of age have been established in a 12-week, double-blind, placebo-controlled study (n=295) [see Clinical Studies (14.3)]. 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).

Responder rates (50% or greater reduction in partial-onset seizure frequency) were a key secondary efficacy parameter and showed numerical improvement with LYRICA compared with placebo: the responder rates were 40.6%, 29.1%, and 22.6%, for LYRICA 10 mg/kg/day, LYRICA 2.5 mg/kg/day, and placebo, respectively.

The most common adverse reactions (≥5%) with LYRICA in this study were somnolence, weight increased, and increased appetite [see Adverse Reactions (6.1)].

The use of LYRICA 2.5 mg/kg/day in pediatric patients is further supported by evidence from adequate and well-controlled studies in adults with partial-onset seizures and pharmacokinetic data from adult and pediatric patients [see Clinical Pharmacology (12.3)].

1 Month to Less than 4 Years of Age with Partial-Onset Seizures
The safety and effectiveness of LYRICA as adjunctive treatment for partial-onset seizures in pediatric patients 1 month to less than 4 years of age have been established in a 14-day double-blind, placebo-controlled study (N=175) [see Clinical Studies (14.3)]. The youngest subject evaluated was 3 months of age; use in patients 1 month to less than 3 months of age is supported by additional pharmacokinetic analyses. Patients treated with LYRICA 14 mg/kg/day had, on average, 43.9% greater reduction in partial-onset seizures than patients treated with placebo (p=0.0223). In addition, pediatric patients treated with LYRICA 14 mg/kg/day showed numerical improvement in responder rates (≥50% reduction in partial-onset seizure frequency) compared with placebo (53.6% versus 41.5%). Patients treated with LYRICA 7 mg/kg/day did not show improvement relative to placebo for either endpoint.

The most common dose-related adverse reactions (>5%) with LYRICA in this study were somnolence, pneumonia, and viral infection [see Adverse Reactions (6.1)].

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*

Date of search	September 13, 2022
Time period of search	August 1, 2018† - September 12, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product active ingredient: Pregabalin
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.
† Data end date of previous DPV-II Pediatric Postmarketing Pharmacovigilance Review for pregabalin was July 31, 2018[9]
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from August 1, 2018, through September 12, 2022, with pregabalin.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 1, 2018 through September 12, 2022 With Pregabalin

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	33,388 (18,721)	18,715 (6,487)	2,229 (744)
Pediatrics (0 - <17 years)	472 (43)	**446 (30)**	**18 (12)**

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

† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

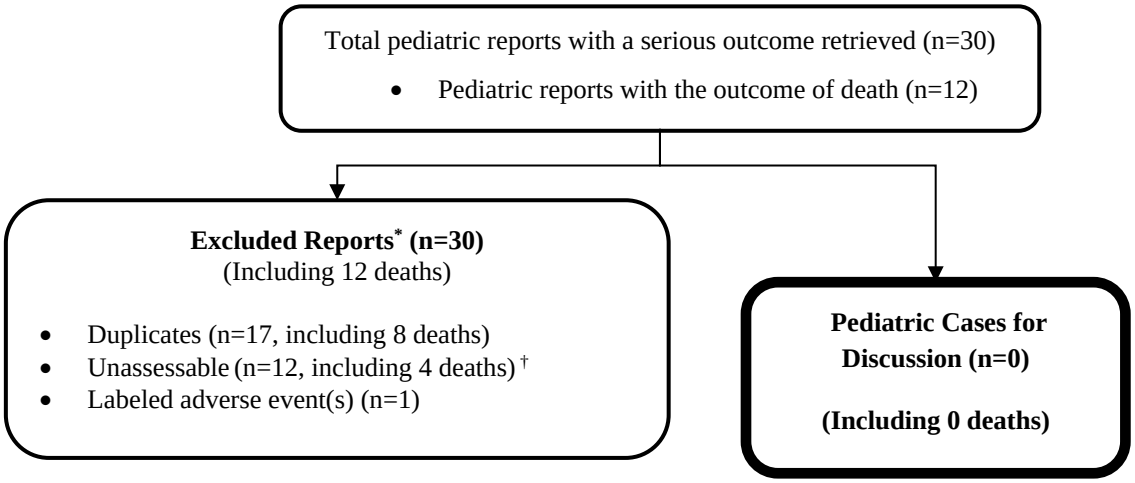
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 30 U.S. serious pediatric reports from August 1, 2018, through September 12, 2022.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as duplicate reports, unassessable reports, or labeled adverse event without new features.

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

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



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

† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified. This included 4 death reports. All 4 death reports provided limited information for causality assessment.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

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

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with pregabalin in the pediatric population.

4 DISCUSSION

We reviewed all FAERS U.S. serious cases with pregabalin in the pediatric population (ages 0 to <17 years) during the period of August 1, 2018, through September 12, 2022. Our evaluation did not identify any cases reporting unlabeled adverse event associated with pregabalin in the pediatric population.

5 CONCLUSION

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

6 RECOMMENDATION

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

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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