Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	January 19, 2024
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Product Name:	Lithium
Pediatric Labeling Approval Date:	October 4, 2018
Application Type/Number:	NDA 017812/031 (lithium carbonate capsules) NDA 018421/031 (lithium oral solution) NDA 018558/026 (lithium carbonate tablets)
Applicant:	West-Ward Pharmaceuticals
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lithium in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on U.S. serious unlabeled adverse events associated with lithium carbonate in pediatric patients.

Lithium is a mood-stabilizing agent first approved in the U.S. on April 6, 1970. There are several lithium products available. Lithium carbonate capsule (NDA 017812), lithium oral solution (NDA 018421, discontinued from marketing but available in generic formulations), lithium carbonate tablet (NDA 018558), and lithium oral solution (NDA 018421) are indicated for monotherapy treatment of bipolar I disorder, treatment of acute manic and mixed episodes in patients 7 years and older, and the maintenance treatment of bipolar I disorder in patients 7 years and older. Lithobid (lithium carbonate) extended-release tablet (NDA 018027) is indicated for the treatment of manic episodes of bipolar disorder and maintenance treatment for individuals with a diagnosis of bipolar disorder. The safety and effectiveness in pediatric patients under 12 years of age have not been determined for Lithobid.

Under BPCA and in collaboration with FDA, the National Institutes of Health (NIH) prioritized lithium as a drug in critical need of improved pediatric labeling. NIH oversaw the fulfilment of two pediatric studies for lithium: COLT1 (NCT00442039, NICHD-2005-07-01) and COLT2 (NCT01166425, NICHD-2005-07-2). Findings from these studies supported the efficacy and safety for lithium carbonate capsule/tablet and lithium oral solution in patients aged 7 – 17 years and informed pediatric dosing recommendations.

Upon completion of COLT1 and COLT2, data from both studies were submitted to FDA and NIH for review. To inform FDA's Division of Psychiatry Products (DPP) review of the COLT1 and COLT2 trial data, the Office of Surveillance and Epidemiology (OSE) performed a postmarketing pharmacovigilance and drug utilization review for lithium focused on pediatric patients aged 7-17 years. OSE's review on March 14, 2016, identified an association between the use of lithium and nephrotic syndrome in both pediatric and adult populations. OSE recommended the addition of nephrotic syndrome to the WARNINGS AND PRECAUTIONS section of the lithium labeling. The lithium product labeling was updated to include nephrotic syndrome under section 5.4 under "Lithium-induced chronic kidney disease." On October 4, 2018, FDA approved the pediatric labeling change that extended the indication of lithium carbonate capsule/tablet and lithium oral solution for use in patients aged 7 – 17 years.

This pediatric postmarketing pharmacovigilance review was prompted by the lithium pediatric labeling on October 4, 2018. DPV has not previously presented a postmarketing pharmacovigilance review for lithium carbonate for the Pediatric Advisory Committee

DPV searched FAERS for all U.S. serious reports with lithium carbonate in pediatric patients less than 18 years of age from January 21, 2016 – November 5, 2023, and identified 53 reports. However, DPV excluded all reports from further discussion. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with lithium carbonate in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for lithium carbonate at this time and will continue routine pharmacovigilance monitoring for lithium carbonate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lithium in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on U.S. serious unlabeled adverse events associated with lithium carbonate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lithium is a mood-stabilizing agent first approved in the U.S. on April 6, 1970. There are several lithium products available. See **Table 1** for a list of currently available lithium products approved by FDA.

Table 1. Lithium Products, Formulation, Indication for Use

Product Name/ NDA/ Formulation	Indication for Use	Pediatric Indication
Lithium carbonate NDA 017812[1] Capsule	Monotherapy for the treatment of bipolar I disorder - Treatment of acute manic and mixed episodes in patients 7 years and older - Maintenance treatment in patients 7 years and older	Yes
Lithium NDA 018421[*2] Oral solution	Monotherapy for the treatment of bipolar I disorder - Treatment of acute manic and mixed episodes in patients 7 years and older - Maintenance treatment in patients 7 years and older	Yes
Lithium carbonate NDA 018558[3] Tablet	Monotherapy for the treatment of bipolar I disorder - Treatment of acute manic and mixed episodes in patients 7 years and older - Maintenance treatment in patients 7 years and older	Yes
Lithobid (lithium carbonate) NDA 018027[4] Tablet, extended release	Treatment of manic episodes of bipolar disorder Maintenance of treatment for individuals with a diagnosis of bipolar disorder	Yes[†]

[*] The original application for lithium oral solution (NDA 018421) is currently discontinued from marketing[5] but generic formulations are available (ANDA 070755, 218036)

[†] The *Pediatric Use* subsection of the Lithobid labeling states that safety and effectiveness in pediatric patients under 12 years of age have not been determined and its use in these patients is not recommended.

Abbreviation: NDA=New Drug Application

Under BPCA and in collaboration with FDA, the National Institutes of Health (NIH) prioritized lithium as a drug in critical need of improved pediatric labeling. On September 26, 2003, FDA issued a Written Request (WR) to the Sponsor of the approved applications for lithium (NDA 017812, 018421, 018558) to complete 1) a pediatric pharmacokinetic and tolerability study, and 2) a pediatric efficacy and safety study with pharmacokinetic assessments.[6] The Sponsor declined to conduct these studies and FDA referred the WR to NIH who ultimately oversaw the fulfilment of two pediatric studies:

- COLT1 (NCT00442039, NICHD-2005-07-01) "Pediatric Pharmacokinetic and Tolerability Study of Lithium for the Treatment of Pediatric Mania Followed by an

Open Label Long Term Safety Period, Discontinuation Phase, and Restabilization Period"[7]

- COLT2 (NCT01166425, NICHD-2005-07-2) "A Randomized, Double Blind, Placebo Controlled Study of the Efficacy of Lithium for the Treatment of Pediatric Mania followed by an Open Label Long-Term Safety Period, Double-Blind, Placebo-Controlled Discontinuation Phase, and Open Label Restabilization Period."[8]

Findings from these studies supported efficacy and safety for lithium carbonate capsule/tablet and lithium oral solution in patients aged 7 – 17 years and informed pediatric dosing recommendations.

Upon completion of COLT1 and COLT2, data from both studies were submitted to FDA and NIH for review. To inform FDA's Division of Psychiatry Products (DPP)[a] review of the COLT1 and COLT2 trial data, the Office of Surveillance and Epidemiology (OSE) performed a postmarketing pharmacovigilance and drug utilization review for lithium focused on pediatric patients aged 7-17 years. OSE's review on March 14, 2016, identified an association between the use of lithium and nephrotic syndrome in both pediatric and adult populations. OSE recommended the addition of nephrotic syndrome to the WARNINGS AND PRECAUTIONS section of the lithium labeling.[9] The lithium product labeling was updated to include nephrotic syndrome under section 5.4 under "Lithium-induced chronic kidney disease."[10] On October 4, 2018, FDA approved the pediatric labeling change that extended the indication of lithium carbonate capsule/tablet and lithium oral solution for use in patients aged 7 – 17 years.[11]

This pediatric postmarketing pharmacovigilance review was prompted by the lithium pediatric labeling on October 4, 2018. DPV has not previously presented a postmarketing pharmacovigilance review for lithium carbonate for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The lithium carbonate capsule/tablet (NDA 017812, 018558) and lithium oral solution (NDA 018421) labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional lithium labeling information, please refer to the full prescribing information.[1,2,3]

WARNING: LITHIUM TOXICITY
See full prescribing information for complete boxed warning.
Lithium toxicity is closely related to serum lithium concentrations, and can occur at doses close to therapeutic concentrations. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (2.3, 5.1).

---------- CONTRAINDICATIONS ----------
Known hypersensitivity to any inactive ingredient in the drug product. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Lithium-Induced Polyuria: May develop during initiation of treatment. Increases risk of lithium toxicity. Educate patient to avoid dehydration. Monitor for lithium toxicity and metabolic acidosis. Discontinue lithium or treat with amiloride as a therapeutic agent (5.2).

[a] The Division of Psychiatric Products was renamed the Division of Psychiatry after the Office of New Drugs reorganization in April 2020.

- Hyponatremia: Symptoms are more severe with faster-onset hyponatremia. Dehydration from protracted sweating, diarrhea, or elevated temperatures from infection increases risk of hyponatremia and lithium toxicity. Educate patients on maintaining a normal diet with salt and staying hydrated. Monitor for and treat hyponatremia and lithium toxicity, which may necessitate a temporary reduction or cessation of lithium and infusion of serum sodium (5.3).
- Lithium-Induced Chronic Kidney Disease: Associated with structural changes in patients on chronic lithium therapy. Monitor kidney function during treatment with lithium (5.4).
- Encephalopathic Syndrome: Increased risk in patients treated with lithium and an antipsychotic. Monitor routinely for changes to cognitive function (5.5).
- Hypothyroidism and Hyperthyroidism: Monitor thyroid function regularly (5.7).
- Hypercalcemia and Hyperparathyroidism: Associated with long-term lithium use. Monitor serum calcium (5.8).

---------- ADVERSE REACTIONS ----------
Common Adverse Reactions:
- Adult Patients: fine hand tremor, polyuria, mild thirst, nausea, general discomfort during initial treatment (6)
- Pediatric Patients (7-17 years): nausea/vomiting, polyuria, thyroid abnormalities, tremor, thirst/polydipsia, dizziness, rash/dermatitis, ataxia/gait disturbance, decreased appetite, and blurry vision (6)

8.4 Pediatric Use

The safety and effectiveness of lithium for monotherapy treatment of acute manic or mixed episodes of bipolar I disorder and maintenance monotherapy of bipolar I disorder in pediatric patients ages 7 to 17 years of age have been established in an acute-phase clinical trial of 8 weeks in duration followed by a 28-week randomized withdrawal phase [see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)].

The safety and effectiveness of lithium has not been established in pediatric patients less than 7 years of age with bipolar I disorder.

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	November 6, 2023
Time period of search	January 21, 2016[†] – November 5, 2023
Search type	RxLogix Quick Query
Product terms	Product active ingredient: lithium carbonate[‡]
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data lock date from last pediatric postmarketing pharmacovigilance review for lithium ‡ The FAERS search focused on lithium carbonate as this is the only lithium active ingredient with marketed NDAs. A separate FAERS search conducted using lithium citrate as the product active ingredient did not yield any pediatric reports. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

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 January 21, 2016 – November 5, 2023, with lithium carbonate.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From January 21, 2016 – November 5, 2023, With Lithium Carbonate

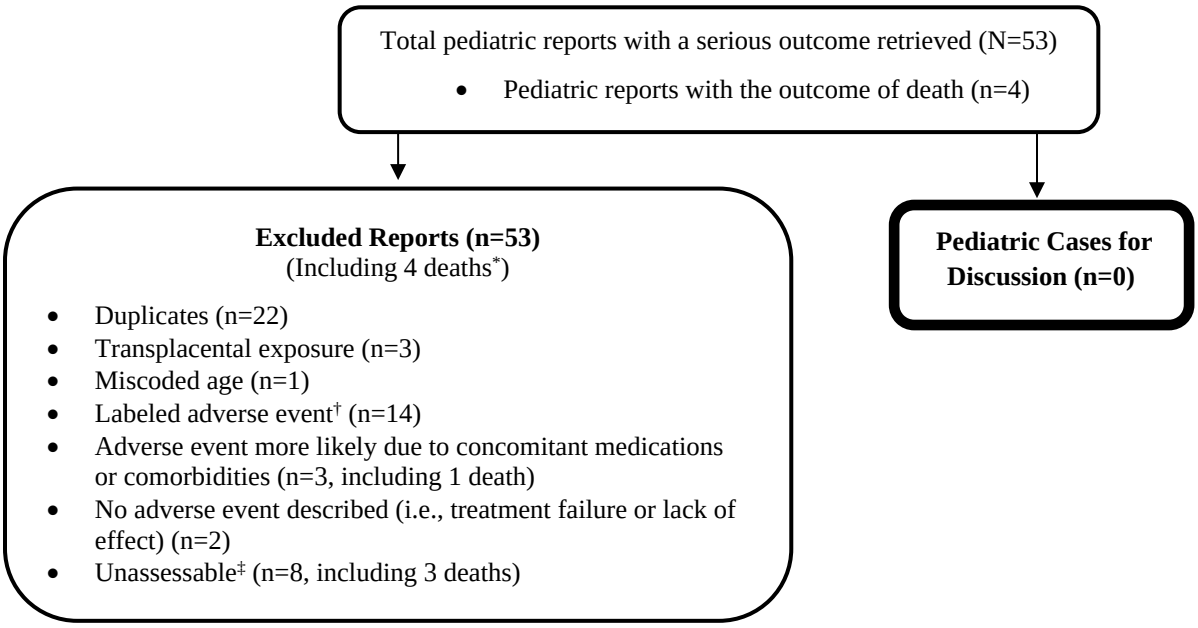
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	3244 (523)	3134 (433)	207 (88)
Pediatrics (0 - < 18 years)	223‡ (63)	213‡ (53)	13‡ (4)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. Ten additional reports of pediatric death were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 53 U.S. serious pediatric reports from January 21, 2016 – November 5, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 53 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Lithium Carbonate



* Four excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to lithium carbonate. In one case, fatal outcome was attributable to another product (overdose ingestion of a hallucinogen drug). Causality was unassessable in three cases as there was insufficient evidence to determine if lithium contributed to the fatal events. Of the unassessable cases, one case described a 16-year-old patient who completed suicide after ingestion of multiple drug products including lithium, one case described a 17-year-old patient who died after polysubstance drug abuse from a presumed overdose of illicit substances and medications including lithium, and one case described a law enforcement investigation into an infant death where exposure to lithium was unknown.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The 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.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with lithium carbonate in pediatric patients less than 18 years of age from January 21, 2016 – November 5, 2023, and identified 53 reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with lithium carbonate in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for lithium carbonate at this time and will continue routine pharmacovigilance monitoring for lithium carbonate.

6 REFERENCES

1. Lithium carbonate capsules. [Prescribing information]. Eatontown, NJ; West-Ward Pharmaceuticals Corp.: October 2022.
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8. National Institute of Child Health and Human Development Data and Specimen Hub (DASH). A Randomized, Double-Blind, Placebo Controlled Study of the Efficacy of Lithium for Treatment of Pediatric Mania followed by an Open Label Long-Term Safety Period, Double-Blind, Placebo-Controlled Discontinuation Phase and Open Label Restabilization Period (BPCA COLT2). Available at: https://dash.nichd.nih.gov/Study/16020. Accessed on November 7, 2023.
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10. Lithium carbonate oral solution, tablets, capsules. [Prescribing information]. Columbus, OH; Roxane Laboratories, Inc.: October 2016.
11. Approval Letter. NDA 17812/S-031, NDA 18421/S-031, NDA18558/S-026. October 4, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/017812Orig1s031,018421Orig1s031,018558Orig1s026ltr.pdf

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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