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

Pediatric Postmarketing Pharmacovigilance Review

Date:	February 27, 2025
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Product Name:	Latuda (lurasidone hydrochloride)
Pediatric Labeling Approval Date:	December 4, 2019
Application Type/Number:	NDA 200603
Applicant:	Sunovion Pharms Inc.
TTT Record ID:	2024-10853

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Latuda (lurasidone hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with lurasidone in pediatric patients.

Latuda (lurasidone hydrochloride) is an atypical antipsychotic that was initially approved in the U.S. on October 28, 2010. Lurasidone is currently indicated for:

- Schizophrenia in adults and adolescents (13 to 17 years)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults and pediatric patients (10 to 17 years) as monotherapy
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate.

This pediatric postmarketing safety review was stimulated by pediatric labeling on December 4, 2019, that included information from a postmarket, long-term, open-label safety study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder.

DPV reviewed all U.S. serious FAERS reports with lurasidone in pediatric patients less than 18 years of age from April 16, 2019, through December 25, 2024, and identified 128 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with lurasidone in pediatric patients less than 18 years of age. DPV did not identify any new pediatric safety concerns for lurasidone at this time and will continue routine pharmacovigilance monitoring for lurasidone.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Latuda (lurasidone hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with lurasidone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Latuda (lurasidone hydrochloride) is an atypical antipsychotic that was initially approved in the U.S. on October 28, 2010. Lurasidone is currently indicated for:[1]

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This pediatric postmarketing safety review was stimulated by pediatric labeling on December 4, 2019, that included information from a postmarket, long-term, open-label safety study of lurasidone in the treatment of pediatric patients (ages 10 to 17 years) with a diagnosis of depressive episode associated with bipolar disorder.[2]

On August 8, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for lurasidone in pediatric patients. DPV identified QT prolongation, aggression with or without psychosis, and tremor as adverse events of interest, but there was insufficient evidence to suggest a new safety signal. DPV recommended to continue routine monitoring for all adverse events with lurasidone including QT prolongation.[3] On September 19, 2019, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.[4]

1.2 RELEVANT LABELED SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).
- Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors. (5.2).

The lurasidone labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[1] For additional lurasidone labeling information, please refer to the full prescribing information.

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

- Known hypersensitivity to LATUDA or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (2.6, 4, 7.1).
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (2.6, 4, 7.1).

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

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.3).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4).
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.5).
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6).
- Hyperprolactinemia: Prolactin elevations may occur (5.7).
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing LATUDA if a clinically significant decline in WBC occurs in the absence of other causative factors (5.8).
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.9).

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

Commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) were (6.1):

- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13-17 years) with schizophrenia: somnolence, nausea, akathisia, EPS (non-akathisia), rhinitis (80mg only), and vomiting
- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Pediatric patients (10-17 years) with bipolar depression: nausea, weight increase, and insomnia.

8.4 Pediatric Use

Schizophrenia
The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients *[see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14.1)].*

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with schizophrenia.

Bipolar Depression
The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.2)].*

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 10 years of age with bipolar depression.

Irritability Associated with Autistic Disorder
The effectiveness of LATUDA in pediatric patients for the treatment of irritability associated with autistic disorder has not been established.

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorder s, 4th Ed., Text Revision [DSM-IV-TR] criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 20mg, 14/51 or 27% for 60mg, and 2/49 or 4% for placebo), particularly in children ages 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

In a long-term, open-label study that enrolled pediatric patients (age 6 to 17 years) with schizophrenia, bipolar depression, or autistic disorder from three short-term, placebo-controlled trials, 54% (378/701) received lurasidone for 104 weeks. There was one adverse event in this trial that was considered possibly drug-related and has not been reported in adults receiving lurasidone: a 10 year old male experienced a prolonged, painful erection, consistent with priapism, that led to treatment discontinuation.

In this trial, the mean increase in height from open-label baseline to Week 104 was 4.94 cm. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex-matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, the mean change in height z-score from open-label baseline to Week 104 was +0.05 SD, indicating minimal deviation from the normal growth curve.

Juvenile animal studies

Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m^2. Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m^2. The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m2. In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m^2. Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m^2 and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m2. Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MRHD based on mg/m^2 and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m^2.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	December 26, 2024
Time period of search	April 16, 2019† - December 25, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Lurasidone, lurasidone hydrochloride
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for lurasidone ended on April 15, 2019.
‡ 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.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America

3 RESULTS

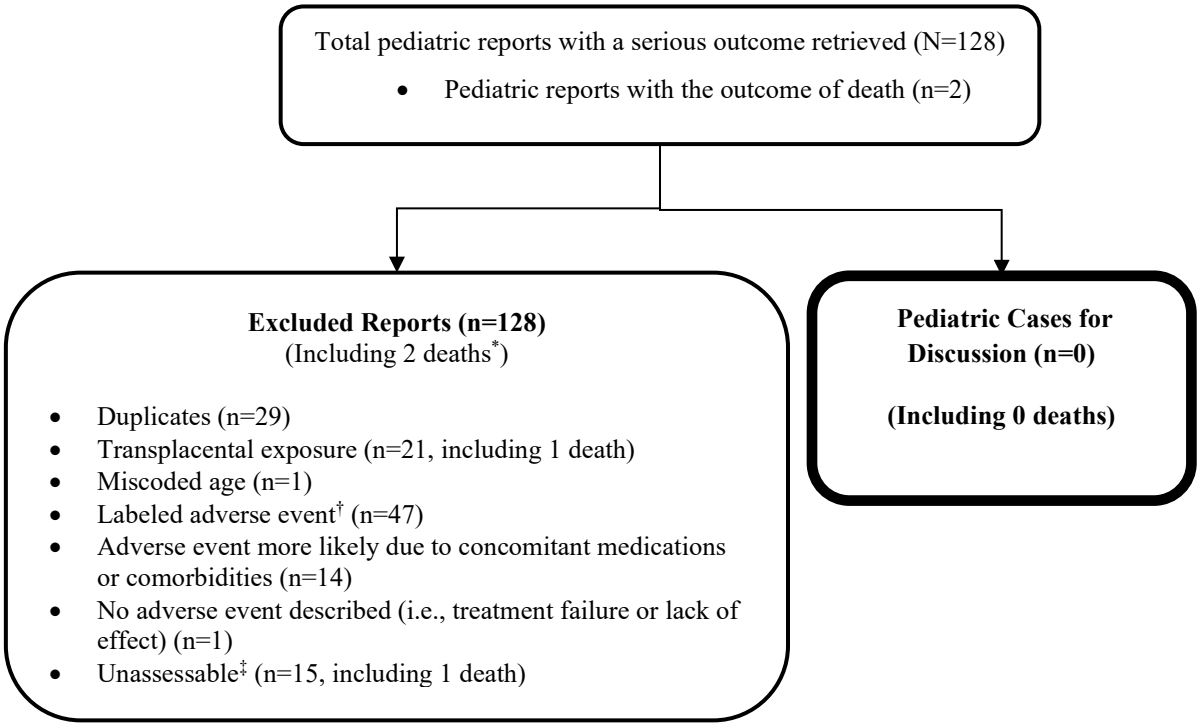
3.1 FAERS

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

Our FAERS search retrieved 128 U.S. serious pediatric reports for patients less than 18 years old from April 16, 2019, through December 25, 2024.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 128 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

[a] Includes one pediatric report that was identified among reports not coded with an age.

Figure 1. Selection of U.S. Serious Pediatric Cases With Lurasidone



* Two excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to lurasidone. One case described a 16-year-old female who completed suicide. The patient had a history of bipolar disorder and the report stated the patient's mother "had an aggressive temperament and may have been involved in some way to encourage [the patient] to commit suicide." The other fatal case described a premature neonate with prenatal exposure to lurasidone and lithium who died from an unspecified cardiac disorder.
† Labeled adverse event does not represent increased severity.
‡ 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.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with lurasidone in pediatric patients less than 18 years of age from April 16, 2019, through December 25, 2024, and identified 128 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

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

6 REFERENCES

1. Latuda® (lurasidone hydrochloride) tablets, for oral use [Prescribing Information]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; December 2019.
2. Dubitsky G, Muniz J. Review and Evluations of Clinical Data NDA# 200603 for Latuda (lurasidone HCL) tablets. November 2019. https://www.fda.gov/media/133816/download?attachment
3. Tran T, Kim I, Wu E, Muñoz, M. FDA Office of Surveillance and Epidemiology - Pediatric Postmarketing Pharmacovigilance Review- Latuda (lurasidone hydrochloride). 2019. https://www.fda.gov/media/130835/download.
4. Pediatric Advisory Recommendations and Updates [updated October 2, 2024; cited 2024 December 27]. Available from: https://www.fda.gov/advisory-committees/pediatric-advisory-committee/pediatric-advisory-recommendations-and-updates.

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.