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Pediatric Postmarketing Pharmacovigilance

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Product Name: Latuda (lurasidone hydrochloride)

**Pediatric Labeling
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for lurasidone in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lurasidone in pediatric patients.

The FDA approved Latuda (lurasidone hydrochloride) on October 28, 2010 for the treatment of schizophrenia and on June 28, 2013, FDA approved the indication for the treatment of Bipolar I Disorder (bipolar depression) as monotherapy or as adjunctive therapy with lithium or valproate in adults. FDA approved the expansion of lurasidone's indications to the pediatric population to include the treatment of schizophrenia in adolescents ages 13-17 years (approved on January 27, 2017) and monotherapy treatment of Bipolar I Disorder (bipolar depression) in pediatric patients 10-17 years (approved on March 5, 2018).

We reviewed 62 serious pediatric FAERS reports with lurasidone in the pediatric population through 17 years of age during the period of July 14, 2017 through April 15, 2019. Most reports described labeled adverse events such as suicide, extrapyramidal symptoms, and neuroleptic malignant syndrome, or adverse events with limited information for causality assessment. Of the 62 reports reviewed, we identified four cases describing unlabeled adverse events of interest including aggression with or without psychosis (n=2), QT prolongation (n=1), and tremor (n=1). The two cases of aggression with or without psychosis occurring within 4-6 weeks of starting lurasidone may be explained by underlying disease. The expanded search for pediatric cases of QT prolongation and cardiac events since approval retrieved two total cases of QT prolongation. These cases lacked clinical information such as medical history, QT values at baseline and while on/off lurasidone treatment, and chronology of drug-event to assess clinical significance and drug-event causality. The remaining case of tremor in a neonate did not provide chronology of the event in relation to transmammary exposure, which precluded a meaningful causality assessment.

DPV will continue monitoring for all adverse events associated with the use of lurasidone including QT prolongation.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Latuda (lurasidone hydrochloride) in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with lurasidone in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lurasidone hydrochloride is an atypical antipsychotic with high antagonistic affinity at the dopamine D2 receptor and at the 5-hydroxytryptamine (5-HT) receptors (5-HT2A and 5-HT7). Lurasidone is available in 20, 40, 60, 80, and 120 mg tablets. The recommended starting dose is 40 mg/day for adults and adolescents with schizophrenia, with a recommended maximum dose of 160 mg/day and 80 mg/day, respectively. The recommended starting dose for adults and pediatric patients with bipolar depression is 20 mg/day, titrating up to 120 mg/day and 80 mg/day, respectively.

The FDA approved Latuda (lurasidone hydrochloride) on October 28, 2010 for the treatment of schizophrenia in adults. In this approval letter, FDA issued two postmarketing requirements (PMRs) under PREA for patients ages 13 to 17 years for the treatment of schizophrenia (PMRs 1701-1 and 1701-2).¹ On June 28, 2013, FDA approved the indication for the treatment of Bipolar I Disorder (bipolar depression) in adults as monotherapy or as adjunctive therapy with lithium or valproate. In this approval letter, FDA issued two PMRs under PREA (PMRs 2058-1 and 2058-2) for patients ages 10 to 17 years for the treatment of bipolar depression.²

Below is the summary from the pediatric clinical trials for the pediatric indications:

- On July 29, 2016, the Sponsor submitted Supplemental New Drug Application (sNDA) 26^{3,4} (S-026) to seek approval of lurasidone for the treatment of schizophrenia in adolescents in response to PMRs 1701-1 and 1701-2.¹ On January 27, 2017, FDA approved lurasidone for the treatment of schizophrenia in adolescents ages 13-17 years.⁵ Below is the FDA's clinical reviewer's summary of the efficacy and safety data.
 - The Sponsor submitted pediatric pharmacokinetic (PK) study (D1050300^a) and clinical efficacy and safety studies, D1050301^b and D10503202,^c (S-026)³ to support the efficacy and safety claims for schizophrenia in the adolescent population (ages 13 to 17 years old). Lurasidone 40 mg and 80 mg were compared to placebo using the primary endpoint of change in baseline to week 6

^a D1050300: Phase 1, open-label, multi-center, single and multiple ascending dose trial to characterize the lurasidone PK profile, safety, and tolerability in subjects ages 6 to 17 years old with schizophrenia, bipolar, autistic, or other psychiatric disorders. Doses of 20, 40, 80, 120, and 160 mg daily were used.

^b D1050301: Phase 3, 6-week randomized double-blind placebo-controlled efficacy and safety study in adolescent subjects with schizophrenia at 40 to 80 mg lurasidone.

^c D1050302: Phase 3, 6-month open-label extension safety study for completers of D1050301 and D1050325 on lurasidone. The final study report of this study was submitted on May 31, 2019 (see Supplement 35).

on the Positive and Negative Syndrome Scale (PANSS) total score. The study showed overall statistical efficacy on the primary endpoint for both lurasidone at both 40 mg and 80 mg doses with analyses suggesting no additional benefit of 80 mg over 40 mg. However, there does appear to be a dose-response relationship for certain safety parameters (e.g., shift from normal to high prolactin, weight gain). The adverse events that occurred at $\geq 5\%$ rate and greater than twice that of placebo included somnolence/sedation, nausea, vomiting, akathisia, extrapyramidal symptoms (non-akathisia), and rhinorrhea/rhinitis (80 mg only). The adverse events identified were expected from prior lurasidone studies and current labeling.

- On May 5, 2017, the Sponsor submitted sNDA (S-029) in response to the PMR 2058-1 to seek approval of lurasidone in the treatment of children and adolescents with major depressive episode associated with bipolar I disorder (bipolar depression) as monotherapy.⁶ On March 5, 2018, FDA approved lurasidone as monotherapy for the treatment of bipolar depression in children and adolescents (10 to 17 years) based on the evaluation of Sponsor's sNDA 29 (S-029).^{5,7} Below is the FDA's clinical reviewer's summary of the relevant efficacy and safety data for this pediatric indication:
 - The Sponsor conducted D1050326^d to evaluate the efficacy and safety of lurasidone 20 to 80 mg/day in the pediatric population (10 to 17 years old). The study demonstrated robust efficacy on the primary and key secondary endpoints of Children's Depression Rating Scale, Revised (CDRS-R) total score and Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP-S) score, respectively. The change from baseline to six weeks on both endpoints showed statistical significant with a p-value of <0.0001 . The most common adverse reactions compared to placebo were nausea (16%), somnolence (9%), weight gain (7%), and vomiting (6%). The safety findings were consistent with the lurasidone current labeling.⁷

- (b) (4)

DPV has not previously presented postmarketing adverse event reports for lurasidone in pediatric patients before the Pediatric Advisory Committee. As part of S-029's evaluation, the Division of Psychiatry Products (DPP) consulted DPV to evaluate postmarketing adverse event reports to provide an overall safety profile in pediatric patients less than 18 years of age.⁸ DPV's evaluation identified the potential safety signals of serious risks including severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) and serotonin syndrome.^{8,9}

^d D1050326: 6-week, double-blind, randomized, placebo-controlled, flexible dose, parallel-group study

1.2 RELEVANT LABELED SAFETY INFORMATION

The labeling for lurasidone dated March 2018 contains the following select safety information.¹⁰

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).

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [see *Adverse Reactions* (6.1)].
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) [see *Drug Interactions* (7.1)].
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *Drug Interactions* (7.1)].

5 WARNINGS AND PRECAUTIONS

5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack)

5.4 Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring

5.5 Tardive Dyskinesia: Discontinue if clinically appropriate

5.6 Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain

5.7 Hyperprolactinemia: Prolactin elevations may occur

5.8 Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with 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.

5.9 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.

5.10 Falls

Latuda may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

8 USE IN SPECIFIC POPULATIONS

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 Disorders, 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).

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/m². 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/m². 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/m². Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m² 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/m² 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/m².

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

ECG Changes

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel-dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively,

observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship. In short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

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	04/16/2019
Time Period of Search	07/14/2017 [†] - 04/15/2019
Search Type	<i>Product Manufacturer Reporting Summary, Quick Query</i>
Product Terms	Product active ingredient: lurasidone; lurasidone hydrochloride
MedDRA Search Terms (Version 21.1)	All Preferred Terms (PT)
* See Appendix A for a description of the FAERS database.	
[†] Datalock date from previous DPV postmarketing pediatric safety review in patients < 18 years of age [§]	

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 July 14, 2017 through April 15, 2019 with lurasidone.

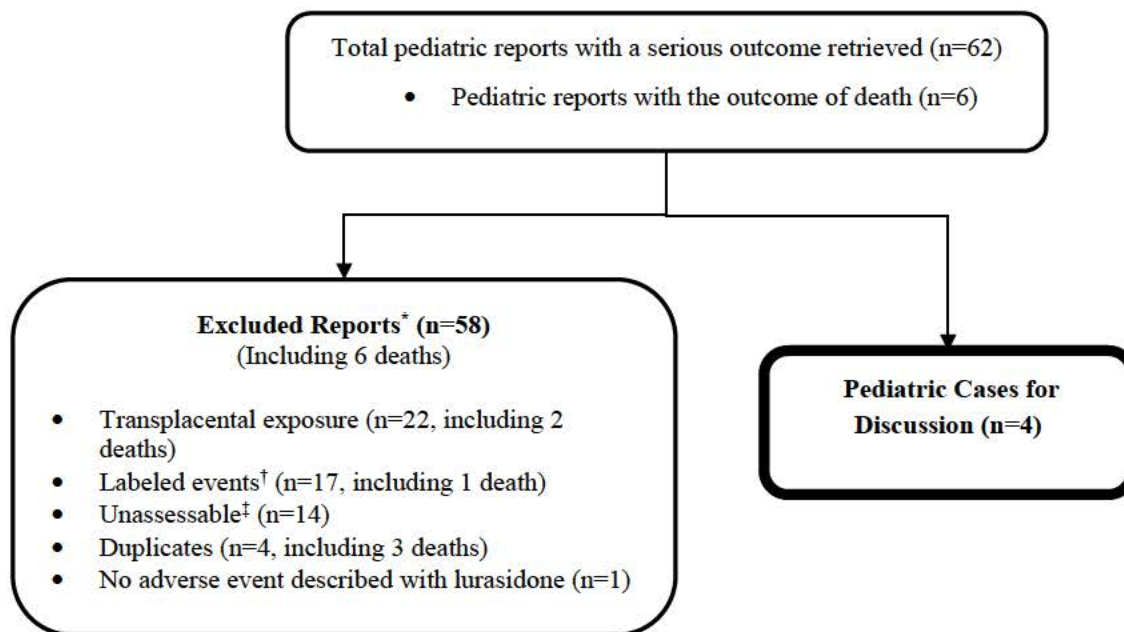
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from July 14, 2017 to April 15, 2019 with Lurasidone			
	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	1,245 (1,090)	585 (434)	109 (100)
Pediatrics (0 - <18 years [‡])	158 ^{§,} (153)	62[§] (58)	6 [§] (6)
<p>* May include duplicates and transplacental exposures, and have not been assessed for causality</p> <p>[†] 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.</p> <p>[‡] Pediatric clinical studies included patients up to 17 years of age.</p> <p>[§] Report counts include three additional reports of pediatric deaths that were identified among reports not reporting an age.</p> <p> Although the focus of the review is on pediatric reports with serious outcomes, we screened most commonly reported PTs in reports with non-serious outcomes for new potential safety signals. This additional screening of non-serious pediatric cases did not result in any new safety signals.</p>			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 62 pediatric reports with a serious outcome from July 14, 2017 to April 15, 2019.

We reviewed all FAERS pediatric reports with a serious outcome. We excluded reports from discussion for various reasons, such as labeled adverse events, adverse events more likely due to underlying disease, or unassessable because of insufficient clinical description of the adverse events. We summarize the remaining cases in the sections below. Figure 1 presents the selection of cases for further discussion.

Figure 1. Selection of Serious Pediatric Cases with Lurasidone



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

† Labeled events include suicide with one case reporting completed suicide (n=5), mania or hypomania (n=3), allergic reaction (n=3), metabolic changes such as weight gain and increase in prolactin levels (n=3), extrapyramidal symptoms including tremor and dystonia (n=2), and neuroleptic malignant syndrome (NMS) (n=1).

‡ Unassessable: Report cannot be assessed for causality because there was insufficient information reported (e.g., unknown time to event, concomitant medications and comorbidities, clinical course and outcome).

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event reports for further discussion (see Figure 1 for reasons for exclusion).

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=4)

We identified four non-fatal, serious FAERS cases with lurasidone in the pediatric population. The four cases described aggression with or without psychosis (n=2), QT prolongation (n=1), and tremor (n=1). Below is the narrative summary of the four cases:

Aggression with or without Psychosis (n=2)

1. FAERS# 15013133v1/MFR# IT-SUNOVION-2018SUN002421/Italy/Hospitalization/Other Serious/June 2018

A physician reported that a 17-year-old female patient experienced pyramidal tract syndrome, distal tremors in the upper limbs, and aggression one month after initiating lurasidone 111 mg (3 tablets of 37 mg) once daily for schizoaffective disorder. The patient's concomitant medications included lansoprazole, quetiapine, nitrazepam (a benzodiazepine), and lorazepam. The patient was hospitalized and lurasidone dose was reduced and subsequently discontinued secondary to the events. Event outcomes were not reported. No other history or clinical information was reported.

Reviewer's comments: Extrapyramidal symptoms including tremors are labeled in the Adverse Reactions section of lurasidone's label. Aggression is not a labeled adverse event for lurasidone. Aggression is not a hallmark feature of schizoaffective disorder per se, but it can be a symptom of schizophrenia spectrum disorders.¹¹ The case lacks detail about the patient's baseline symptoms. Causality assessment for lurasidone remains difficult as it is not possible to assess the extent to which aggression reflects the patient's underlying condition or drug effect.

2. FAERS# 14978914v1/MFR# US-SUNOVION-2015SP000445/U.S./Hospitalization/June 2018

An investigator from a clinical study^e reported a 16-year-old male subject who experienced psychosis and increased aggression requiring hospitalization after 36 days of lurasidone 80mg daily therapy. The subject took lurasidone for schizophrenia. The subject's relevant medical history included psychosis, aggression symptoms of schizophrenia, mood disorder, and insomnia and concomitant medications included melatonin and promethazine. The mother described that the subject was taken to the emergency department by the local police due to aggression towards himself and threatening behavior towards family members. Additionally, the subject experienced loose associations with possible visual hallucinations. During the hospitalization, the subject did not receive lurasidone and was treated with ziprasidone 60 mg orally twice daily. The event was reported as resolved and the subject was discharged from the hospital.

^e Protocol number D1050302, "A 104 Week, Flexible-Dose, Open-Label, Multicenter, Extension Study to Evaluate The Long Term Safety and Effectiveness of Lurasidone in Pediatric Subjects"

Reviewer's comments: Individuals with schizophrenia are vulnerable to early relapse in the first 4 to 6 weeks of therapy with atypical antipsychotic medication.¹² The time-to-onset of psychosis and aggression of 36 days after initiating lurasidone suggests that relapse is possible explanation of symptoms. It is also possible that these symptoms reflect baseline disease and drug ineffectiveness. Without additional information about baseline disease and concurrent exposures, it is not possible to perform a more detailed causality analysis.

QT Prolongation

1. FAERS# 16068424v1/MFR# US-SUNOVION-2019SUN001015/U.S./Other Serious/March 2019

A nurse reported an 11-year-old female patient with bipolar disorder whose disease was unresponsive to aripiprazole. Subsequently, the patient was switched from aripiprazole to lurasidone 40mg (unknown frequency). Lurasidone dose was increased to 60 mg (frequency not specified). On an unknown date, the patient was hospitalized and experienced QTc prolongation (value not specified). Lurasidone was lowered to an unspecified dose secondary to the event. However, QTc prolongation continued after the hospital discharge. Lurasidone was discontinued resulting in resolution of QTc prolongation. Concomitant medications were listed as sertraline and aripiprazole even though it was reported that patient was switched from aripiprazole to lurasidone.

Reviewer's comments: The case did not provide values for baseline QTc and change in QTc interval to assess clinical significance. Lurasidone's package insert mentioned that "in short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with lurasidone or placebo." The time-to-onset for drug-induced QT prolongation is generally short;¹³ however, this case did not provide time-to-onset to assess temporal relationship and to exclude the possible contributory role of aripiprazole. Alternative explanations for QT prolongation include previously unrecognized underlying QT abnormality or concomitant use of sertraline, which is labeled for QT prolongation.¹⁴

For completeness, we conducted an additional search for reports of QT prolongation and cardiac arrhythmia associated with QT prolongation (i.e., torsade de pointes, cardiac arrest, ventricular fibrillation) in pediatric patients since lurasidone approval. The search retrieved another pediatric case (FAERS# 12281469v1 submitted in April 2016 prior to the FAERS search period for this review) of a 14-year-old male on multiple concomitant medications with limited information on medical history, QT values, and chronology of event to assess drug-event causality. We did not identify any pediatric cases of cardiac arrhythmias associated with QT prolongation reported with lurasidone from the additional FAERS search.

Tremor

1. FAERS# 14094255v2/MFR# US-SUNOVION-2017SUN004372/U.S./Hospitalization/October 2017

A consumer reported a 5-week-old infant male experienced tremors after transplacental and possible transmammary exposure to lurasidone. The mother started lurasidone 5 mg twice daily from the third month through the entire pregnancy. The infant (unknown gestational age) was born weighing six pounds with a length of 19.5 inches and head circumference of 32 inches. During the first two weeks after birth, the patient experienced tremors. The tremors stopped for two weeks and reappeared when the patient was 5-week-old. The infant was hospitalized when the tremors recurred and underwent an electroencephalogram and brain scan. EEG ruled out seizures. At unknown time after the delivery and unknown temporal relationship to the adverse event, the patient's mother began breastfeeding with the physician's concurrence and initiated lurasidone 10 mg (1/2 tablet of 20 mg, unspecified frequency). The patient was discharged from the hospital and the outcome of the event was considered unresolved. The mother discontinued lurasidone due to the event.

Reviewer's comments: Tremor in neonates with transplacental exposure of lurasidone during the third trimester is labeled in the Use in Specific Populations section of the lurasidone package insert. Lurasidone is present in rat milk; however, the presence of lurasidone in human milk, the effects on the breastfed infant, or the effects on milk production in human have not been studied.¹⁰ The chronology of events, including implied break in lurasidone therapy, length of breastfeeding, and re-emergence of tremors at 5 weeks of age is unclear and thus obfuscates the transmammary exposure to lurasidone. Newborns have excessive movements that may be normal, such as moro reflex, or abnormal. The differential diagnosis for tremors in a neonate is broad and includes electrolyte, hormonal, or neurological abnormalities.¹⁵ Lack of information about other diagnostic tests, history of concomitant exposures, and developmental history preclude further causality assessment.

4 DISCUSSION

We reviewed 62 serious pediatric FAERS reports with lurasidone in the pediatric population through 17 years of age during the period of July 14, 2017 through April 15, 2019. Most reports described labeled adverse events such as suicide, extrapyramidal symptoms, and neuroleptic malignant syndrome, or adverse events with limited information for causality assessment. Of the 62 reports reviewed, we identified four cases describing unlabeled adverse events of interest including aggression with or without psychosis (n=2), QT prolongation (n=1), and tremor (n=1). The two cases of aggression with or without psychosis occurring within 4-6 weeks of starting lurasidone may be explained by underlying disease. The expanded search for pediatric cases of QT prolongation and cardiac events since approval retrieved two total cases of QT prolongation. These cases lacked clinical information such as medical history, QT values at baseline and while on/off lurasidone treatment, and chronology of drug-event to assess clinical significance and drug-event causality. The remaining case of tremor in a neonate did not provide chronology of

the event in relation to transmammary exposure, which precluded a meaningful causality assessment.

5 CONCLUSION

We identified four adverse events of interest including QT prolongation, aggression with or without psychosis, and tremor associated with lurasidone use. However, there is insufficient evidence to suggest a new safety signal at this time.

6 RECOMMENDATION

DPV will continue monitoring for all adverse events associated with the use of lurasidone including QT prolongation.

7 REFERENCES

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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 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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/s/

THAO T TRAN
08/08/2019 03:39:53 PM

IVONE E KIM
08/09/2019 08:40:21 AM

EILEEN WU
08/09/2019 10:09:30 AM

MONICA MUNOZ
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