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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance

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Product Name(s): Ativan Injection (lorazepam injection)

**Pediatric Labeling
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ativan Injection (lorazepam injection) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with lorazepam injection in U.S. pediatric patients.

Lorazepam injection is a benzodiazepine with anxiolytic, sedative, and anticonvulsant effects. On September 30, 1977, FDA approved Ativan (lorazepam) oral tablet for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. The safety and efficacy of lorazepam oral tablet in children of less than 12 years was not established. On July 25, 1980, FDA approved Ativan (lorazepam) injection for the treatment of status epilepticus and preanesthetic uses in adults 18 years and older. The safety and efficacy for status epilepticus remained unestablished in pediatric patients. On May 27, 2016, the sponsor, Wyeth-Ayerst, updated the current Ativan Injection label to include the results of a clinical study that failed to demonstrate efficacy in pediatric patients for status epilepticus. This pediatric labeling change triggered this review. DPV has not previously evaluated postmarketing adverse event reports with a serious outcome for Ativan in pediatric patients.

DPV reviewed all U.S. FAERS reports with lorazepam injection in pediatric patients from birth through age 17 years from July 25, 1980, to July 15, 2018, reporting a serious outcome, and identified one case for discussion. The single report described a child who experienced the labeled adverse event of hallucinations and the unlabeled adverse event oculogyric crisis. Lack of additional information limited causation analysis and an expanded search of the FAERS database did not yield additional reports. Currently there is no evidence to suggest oculogyric crisis is a new safety signal with lorazepam injection.

DPV did not identify new pediatric safety concerns for lorazepam injection and recommends no regulatory action at this time. DPV will continue to monitor all adverse events associated with the use of lorazepam injection, including oculogyric crisis.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ativan Injection (lorazepam injection) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with lorazepam injection in U.S. pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lorazepam injection is a benzodiazepine with anxiolytic, sedative, and anticonvulsant effects. On September 30, 1977, FDA approved Ativan (lorazepam) oral tablet for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. The safety and efficacy of lorazepam oral tablet in children of less than 12 years was not established. On July 25, 1980, FDA approved Ativan (lorazepam) injection for the treatment of status epilepticus and preanesthetic uses in adults 18 years and older. The safety and efficacy for status epilepticus remained unestablished in pediatric patients. On May 27, 2016, the sponsor, Wyeth-Ayerst, updated the current Ativan Injection label to include the results of a clinical study that failed to demonstrate efficacy in pediatric patients (n= 273) ages 3 months to 17 years for status epilepticus. This pediatric labeling change triggered this review.

DPV has not previously evaluated postmarketing adverse event reports with a serious outcome for Ativan in pediatric patients.

1.2 RELEVANT LABELED SAFETY INFORMATION FOR LORAZEPAM INJECTION¹

BOXED WARNING

- **Risks From Concomitant Use With Opioids:** Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Monitor patients for respiratory depression and sedation.

CONTRAINDICATIONS

- Ativan injection is contraindicated in patients with a known sensitivity to benzodiazepines or its vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol), in patients with acute narrow-angle glaucoma, or in patients with sleep apnea syndrome. It is also contraindicated in patients with severe respiratory insufficiency, except in those patients requiring relief of anxiety and/or diminished recall of events while being mechanically ventilated.
- Ativan Injection is contraindicated for use in premature infants because the formulation contains benzyl alcohol.

WARNINGS

- **Risks From Concomitant Use with Opioids:** Concomitant use of benzodiazepines, including ATIVAN Injection, and opioids may result in profound sedation, respiratory depression, coma, and death.
- **Respiratory Depression:** The most important risk associated with the use of ATIVAN Injection in status epilepticus is respiratory depression. Accordingly, airway patency must be assured and respiration monitored closely. Ventilatory support should be given as required.
- **Excessive Sedation**
- **Usage in Preterm Infants and Neonates:** ATIVAN Injection contains benzyl alcohol. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive

amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol ... If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

PRECAUTIONS

- **Information for Patients: Effect of Anesthetic and Sedation Drugs on Early Brain Development . . .** Studies conducted in young animals and children suggest repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains.
- **Drug Interactions:** Interaction with Benzodiazepines and Other CNS Depressants . . . Monitor patients closely for respiratory depression and sedation.
- **Status Epilepticus:** The safety and effectiveness of ATIVAN for status epilepticus have not been established in pediatric patients. A randomized, double-blind, superiority-design clinical trial of ATIVAN versus intravenous diazepam in 273 pediatric patients ages 3 months to 17 years failed to establish the efficacy of ATIVAN for the treatment of status epilepticus. . . ATIVAN Injection contain benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. . . Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.
- **Preanesthetic:** There are insufficient data to support the efficacy of injectable lorazepam as a preanesthetic agent in patients less than 18 years of age.
- **General:** Seizure activity and myoclonus have been reported to occur following administration of ATIVAN Injection, especially in very low birth weight neonates ... There have been reports of possible propylene glycol toxicity (e.g., lactic acidosis, hyperosmolality, hypotension) and possible polyethylene glycol toxicity (e.g., acute tubular necrosis) during administration of ATIVAN Injection at higher than recommended doses. Symptoms may be more likely to develop in patients with renal impairment ... Pediatric patients may exhibit a sensitivity to benzyl alcohol, polyethylene glycol and propylene glycol, components of ATIVAN Injection. The “gasping syndrome”, characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine, has been associated with the administration of intravenous solutions containing the preservative benzyl alcohol in neonates ... although normal therapeutic doses of ATIVAN Injection contain very small amounts of these compounds, premature and low-birth-weight infants as well as pediatric patients receiving high doses may be more susceptible to their effects.

ADVERSE REACTIONS

- **Other Adverse Experiences:** Skin rash, nausea and vomiting have occasionally been noted in patients who have received injectable lorazepam combined with other drugs during anesthesia and surgery.
- **Paradoxical Reactions:** As with all benzodiazepines, paradoxical reactions such as stimulation, mania, irritability, restlessness, agitation, aggression, psychosis, hostility, rage, or hallucinations may occur in rare instances and in an unpredictable fashion.

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	July 16, 2018
Time Period of Search	July 25, 1980 [†] - July 15, 2018
Search Type	Quick Query
Product Terms	Product name: Ativan Product active ingredient: lorazepam
Other Criteria	Product administration route: intravenous (not otherwise specified); intravenous bolus, intravenous drip
* See Appendix A for a description of the FAERS database.	
[†] U.S. approval date	

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 25, 1980 to July 15, 2018 with lorazepam injection.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from July 25, 1980 to July 15, 2018 with Lorazepam Injection			
	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	913 (733)	882 (706)	144 (104)
Pediatrics (0 - <18 years)	178 [‡] (128)	176 [‡] (126)	11 ^{‡§} (7)
* 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.			
[‡] Three additional reports of pediatric deaths were identified among reports not reporting an age. These reports are included in the counts for pediatric reports.			
[§] Two cases of pediatric death were coded as other types of serious outcomes. These reports are included in the counts for pediatric deaths.			

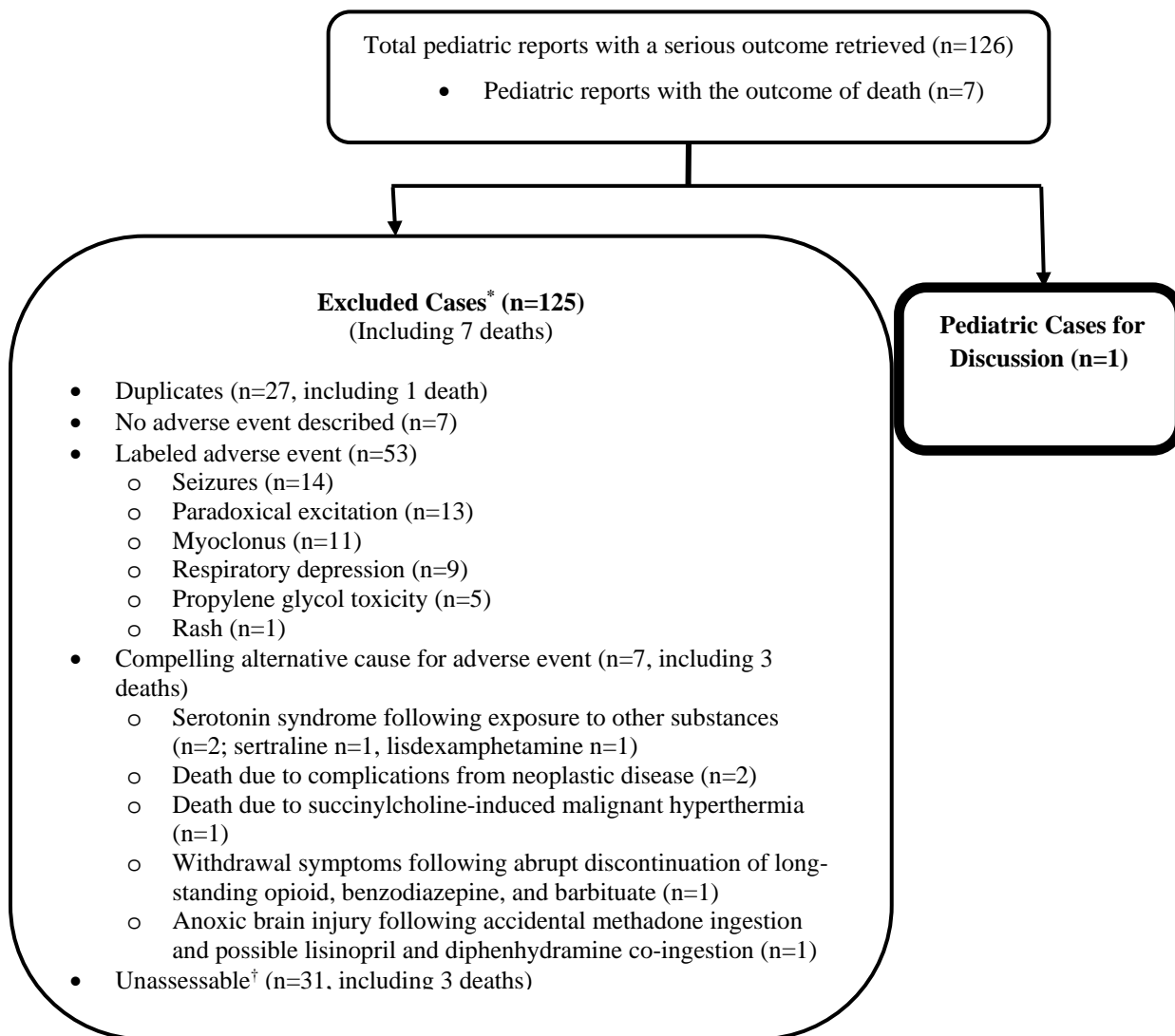
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 126 U.S. FAERS pediatric reports with a serious outcome from July 25, 1980 to July 15, 2018.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. After accounting for duplicate reports (n=27), we excluded reports from further discussion for various reasons such as if the report did not describe an adverse event, if the adverse event was labeled, if the adverse event had compelling alternative etiologies, or if the case was unassessable. We summarize the remaining cases in the sections below.

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

Figure 1. Selection of Serious U.S. Pediatric Cases with Lorazepam Injection



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

[†] Reports 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 case cannot be supplemented or verified.

3.1.3 Summary of Non-Fatal Pediatric U.S. Serious Case (N=1)

We identified one FAERS case with lorazepam injection in the U.S. pediatric population reporting a non-fatal serious outcome. The case is described below.

FAERS Case #4666094, USA, 1989, Other serious important medical event

The report concerned a 9 year old female patient who experienced “hallucinations and oculogyric crisis” after lorazepam injection. No further information was reported.

Reviewer comment: Hallucinations are labeled events for lorazepam in the Adverse Reactions section of the product label.¹ Oculogyric crisis is an acute dystonic reaction involving

extraocular muscles; it is marked by bilateral eye deviation lasting seconds to hours. Oculogyric crisis has been associated with medications such as neuroleptic, benzodiazepine, and anticholinergics products and the condition has also been associated with states of stress and other illnesses.^{2,3} The case lacks additional information including comorbid conditions, concomitant medications, and additional clinical history to aid in the understanding of the clinical picture and causality assessment. For completeness, we searched the FAERS database for additional cases of oculogyric crisis with lorazepam injection in the adult and pediatric population but retrieved no additional case reports.

4 DISCUSSION

We reviewed all U.S. FAERS reports with lorazepam injection in pediatric patients from birth through 17 years from July 25, 1980, to July 15, 2018 reporting a serious outcome, and identified one case for discussion. The single report described the labeled event of hallucinations and the unlabeled adverse event oculogyric crisis. Lack of additional information limited causation analysis and an expanded search of the FAERS database did not yield additional reports. Currently there is no evidence to suggest oculogyric crisis is a new safety signal with lorazepam injection.

5 CONCLUSION

DPV did not identify new pediatric safety concerns for lorazepam injection at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time. DPV will continue to monitor all adverse events associated with the use of lorazepam injection, including oculogyric crisis.

7 REFERENCES

1. Ativan [package insert]. Eatontown, NJ 07724: West-Ward A Hikma Company; April 2017.
2. Solberg M, Koht J. Oculogyric Crises. Louis ED, ed. Tremor and Other Hyperkinetic Movements. 2017;7:491.
3. Koban Y et al. Oculogyric crisis in a patient taking metoclopramide. Clin Ophthalmol. 2014;8:567-569.

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.

8.2 APPENDIX C. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Serious Outcomes*
1	8/4/1989	4666094	1	83245604	Non-Expedited	9	F	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in the following outcome: OT=Other medically significant

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