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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	2
1.1 Product Formulations and Indications.....	2
1.2 Regulatory History	2
1.3 Summary of Relevant Previous FDA Safety Reviews.....	5
1.4 Highlights of Labeled Safety Issues.....	6
1.4.1 Palonosetron.....	6
2 Drug Utilization Data.....	7
2.1 Methods and Materials	7
2.1.1 Determining Settings of Care.....	7
2.1.2 Data Sources Used	8
2.2 Results	8
2.2.1 Number of Patients	8
3 Postmarket Adverse Event Reports	8
3.1 Methods and Materials	8
3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy.....	9
3.2 Results	9
3.2.1 Total Number of FAERS Reports by Age	9
3.2.2 Selection of Pediatric Cases in FAERS	9
3.2.3 Characteristics of Pediatric Case Series.....	10
3.3 Summary of Fatal Pediatric Adverse Event Cases (N=0).....	11
3.4 Summary of Non-Fatal Pediatric Serious Adverse Event Cases (N=4).....	11
4 Discussion.....	13
5 Conclusion	13
6 Recommendations.....	13
7 Appendices.....	14
7.1 Appendix A. Drug Utilization Database Descriptions/Limitations	14
7.2 Appendix B. FAERS.....	14
7.3 Appendix C. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With Drug (N=4).....	15
7.4 Appendix D. Additional FAERS Search Strategy and Results.....	15
8 References.....	16

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports and drug utilization data for Aloxi (palonosetron hydrochloride) in pediatric patients.

Aloxi (palonosetron hydrochloride) injection was approved on July 25, 2003 for use in adults for the following three indications: 1) prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC), 2) prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC), and 3) prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Aloxi (palonosetron hydrochloride) injection was approved on May 27, 2014 for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC in pediatric patients aged 1 month to less than 17 years.

In order to capture pediatric use for palonosetron and to provide context for the adverse event cases submitted to the FDA Adverse Event Reporting System (FAERS) database, drug utilization patterns were assessed. Based on a sample of administrative claims data from June 2014 through November 2016, nearly 100% (321,906 patients) of patients with a prescription and/or medical claim for palonosetron were adults aged 17 years and older. Pediatric patients aged 0-16 years accounted for 0.1% (236 patients) of the sample population. The utilization data for palonosetron was obtained from a sample of pharmacies, clinics, hospitals, and physician offices and are not nationally projected. Nationwide projections are not available at this time.

The Division of Pharmacovigilance (DPV) evaluated all FAERS reports of adverse events in the pediatric population for palonosetron from the initial FDA approval of palonosetron injection in adults on July 25, 2003 to December 1, 2016. The initial approval date was used to capture all reports of off-label use of palonosetron in pediatric patients and all reports occurring after the pediatric labeling date of May 27, 2014. The review of FAERS pediatric reports resulted in identification of four non-fatal cases with a serious outcome. No new safety signals were identified after review of the four cases. Of the four cases, one reported an unlabeled event of extrapyramidal symptoms and three reported a labeled event of hypersensitivity reaction with an additional constellation of symptoms such as dyspnea, diaphoresis, and tachycardia. The single pediatric case of extrapyramidal symptoms did report a temporal association to palonosetron administration; however, the patient was receiving concomitant ifosfamide. Ifosfamide is labeled for central nervous system (CNS) toxicity including extrapyramidal symptoms. The time to onset and resolution of ifosfamide-associated neurotoxicity described in the ifosfamide product label is similar to the timeframe reported in the single pediatric case. The three remaining cases of hypersensitivity reactions described patients who received concomitant chemotherapy agents and because of limited information, it is not possible to attribute the reaction to palonosetron alone. Hypersensitivity reactions are labeled for palonosetron and at this time no additional changes to the label are recommended.

DPV will continue postmarketing surveillance of all adverse events with the use of palonosetron injection in pediatric patients.

1 INTRODUCTION

This review evaluated postmarketing adverse event reports and drug utilization data for Aloxi (palonosetron hydrochloride/NDA 021372) injection in pediatric patients. The approval of palonosetron injection for the prevention of acute chemotherapy-induced nausea and vomiting (CINV) in pediatric patients (aged 1 month to less than 17 years) on May 27, 2014 triggered this review.

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Palonosetron is a serotonin-3 (5-HT₃) receptor antagonist^a available as an intravenous (IV) injection.^{1,b} Palonosetron injection is FDA approved for use in **adults** for the following three indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC)
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery

Palonosetron injection is indicated in **pediatric** patients 1 month to less than 17 years of age for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC chemotherapy.

The recommended dosage of palonosetron IV in **adult** patients for the prevention of CINV and PONV is 0.25 mg once infused over 30 seconds approximately 30 minutes prior to the start of chemotherapy and 0.075 mg once administered over 10 seconds immediately before the induction of anesthesia, respectively. The recommended dosage of palonosetron IV in **pediatric** patients 1 month to less than 17 years of age for the prevention of CINV is 20 mcg/kg once (max 1.5 mg) infused over 15 minutes approximately 30 minutes prior to the start of chemotherapy.

1.2 REGULATORY HISTORY

The major regulatory interactions between the Sponsor and FDA regarding the pediatric clinical studies and approval history for palonosetron in adult and pediatric patients are summarized below.^c

April 24, 2000: The Sponsor submitted a Proposal for Pediatric Study Request (PPSR) to IND 39797 requesting a Written Request (WR) based on plans to perform pediatric study PALO-99-07 in CINV.^d

^a Three other 5-HT₃ receptor antagonists approved by the FDA for use in adult and pediatric patients are: ondansetron, granisetron, and dolasetron.

^b Aloxi (palonosetron) oral soft capsule (NDA 022233) was approved by the FDA on August 22, 2008 for the prevention of acute nausea and vomiting associated with initial and repeat courses of MEC in adult patients. Aloxi (palonosetron) oral soft capsule was never marketed in the U.S., but has been approved and launched in 20 foreign countries.

^c The regulatory history was adapted from Dr. Teresa Buracchio's and Dr. Farrokh Sohrabi's (Division of Gastroenterology and Inborn Errors Products (DGIEP) medical officers) clinical reviews of pediatric supplements S-018 and S-019 (b) (4) CINV indication to pediatric patients aged 1 month to less than 17 years for palonosetron injection.

August 14, 2000: The Sponsor submitted the pediatric study PALO-99-07 protocol and draft study reports for juvenile toxicology studies in rats and dogs to the FDA.

2000-2003: The FDA had concerns about abnormal ocular findings after review of the juvenile toxicology studies and required the sponsor to 1) add ophthalmic exams to the pediatric study PALO-99-07 protocol and 2) repeat the juvenile rat toxicity study.

January 20, 2003: The Sponsor submitted a repeat juvenile rat toxicology study without ocular toxicity findings and requested removal of the ocular testing requirement for the pediatric studies.

July 25, 2003: Palonosetron injection was approved for use in **adults** for the prevention of 1) acute nausea and vomiting associated with initial and repeat courses of MEC and HEC and 2) delayed nausea and vomiting associated with initial and repeat courses of MEC.

November 3, 2003: The FDA was concerned about a potential safety signal of QTc prolongation in some of the first six pediatric patients in pediatric study PALO-99-07, resulting in a partial clinical hold on pediatric study PALO-99-07.

January 9, 2004: The FDA removed the clinical hold after the sponsor agreed to conduct additional cardiac monitoring in pediatric study PALO-99-07 and to complete adult thorough QT study PALO-03-11.

August 3, 2005: In response to the Sponsor's request for deferral of PREA pediatric studies for the CINV indications, the FDA waived the pediatric assessment for birth to <1 month of age because palonosetron is not likely to be used by a substantial number of patients in this age group for the CINV indication. Based on the Sponsor's proposed development plan and timeframe for study completion, the FDA set the pediatric assessment deferral date for the CINV indication to July 31, 2008.

April 27, 2007: The Sponsor submitted supplement-8 (S-008) to the FDA, which contained the results of adult thorough QT study PALO-03-11.

PALO-03-11 was a randomized, single dose, double dummy, parallel group, placebo controlled, and active controlled study evaluating the effect of placebo, moxifloxacin (active control), and IV palonosetron on the QTc interval in adults. The objective was to evaluate the ECG effects of IV palonosetron at single doses of 0.25 mg, 0.75 mg, or 2.25mg, which covered a 9-fold range of exposure. The study demonstrated no significant effect of IV palonosetron at doses up to 2.25 mg on any ECG interval, including QTc duration (cardiac repolarization).

February 29, 2008: Palonosetron injection was approved for the prevention of PONV in **adults**.

July 10, 2008: The protocol for the pediatric PONV study PALO-07-29 was submitted to IND 39797.

November 16, 2009: A teleconference was held to discuss the WR outline. The Sponsor and FDA agreed that pediatric study PALO-99-07 (CINV indication) and pediatric study

^d There were three subsequent amendments to the PPSR made by the sponsor and submitted to the FDA.

PALO-07-29 (PONV (b) (4)) would serve as pilot studies for larger trials to be requested in the WR.

July 22, 2009: The Sponsor submitted the completed pediatric PONV study PALO-07-29 results to the FDA.

2010-2011: The FDA issued a WR, which included two previously conducted pediatric studies (PALO-99-07, PALO-07-29) and included the requirement for larger trials in each indication against a standard of care active comparator (PALO-10-14, PALO-10-20). The WR initially included the requirement for the development of a pharmacy compounded palonosetron liquid preparation for oral administration in prevention of CINV with MEC. There were three subsequent amendments to the WR (September 30, 2010, October 22, 2012, February 15, 2013), of which the requirement for the development of a compounded palonosetron liquid preparation for use in pediatric CINV patients was eliminated.

December 4, 2012: A meeting was held prior to the submission of supplemental NDA (sNDA) between the Sponsor and FDA and the following three points were discussed: 1) the Sponsor would reanalyze the data in pediatric study PALO-99-07 to be in accordance with the pediatric age groups stipulated in the WR, 2) FDA and Sponsor agreed on format and content of the Summary of Clinical Efficacy, Summary of Clinical Safety, and the safety database, and 3) FDA requested that the PONV and CINV indications be submitted as separate sNDAs.

January 16, 2013: The FDA conveyed additional comments and recommendations to the Sponsor in a Type C meeting written response. The FDA had the following three recommendations: 1) the Sponsor should include adverse event tables for pediatrics in the labeling for palonosetron injection even if the adverse event profile of palonosetron injection was found to be similar between pediatrics and adults, 2) the proposed cutoff of $\geq 2\%$ for common adverse events was deemed acceptable, and 3) the sNDA would receive priority review because it was submitted in response to a WR.

November 27, 2013: The Sponsor submitted sNDA 21372/S-018 (PONV) and sNDA 21372/S-019 (CINV).

PONV Studies

PALO-07-29 was a multicenter, double blind, randomized, parallel group, stratified study of two doses of IV palonosetron in patients >28 days to 16 years of age undergoing an elective surgical procedure requiring general endotracheal inhalation anesthesia and receiving nitrous oxide during the maintenance phase of anesthesia. The study was conducted to evaluate the safety and efficacy of two different doses of palonosetron, 1 mcg/kg or 3 mcg/kg, for the prevention of PONV.

PALO-10-14 was a multicenter, double blind, double dummy, randomized, parallel group, stratified study comparing IV palonosetron to IV ondansetron in neonates (0-27 days of age) and children aged less than 17 years. The study was conducted to evaluate the efficacy and safety of IV palonosetron 1 mcg/kg compared to IV ondansetron 0.1 mg/kg for the prevention of PONV.

CINV Studies

PALO-10-20 was a multicenter, randomized, double blind, parallel group study of two different doses of IV palonosetron compared to IV ondansetron in pediatric patients aged from full-term neonates to <17 years undergoing single or repeated cycles of MEC or HEC. The study was conducted to evaluate the safety, tolerability, pharmacokinetics, and efficacy of IV palonosetron 10 mcg/kg or 20 mcg/kg for the prevention of CINV through 120 hours after the start of chemotherapy.

PALO-99-07 was a multicenter, randomized, double blind, parallel, uncontrolled study of two doses of IV palonosetron in patients with cancer >28 days to less than 18 years of age receiving MEC or HEC. The study was conducted to assess the safety, tolerability, pharmacokinetics, and efficacy of IV palonosetron 3 mcg/kg or 10 mcg/kg for the prevention of CINV.

May 27, 2014: Palonosetron injection was approved for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC in **pediatric** patients aged 1 month to less than 17 years. (b) (4)

1.3 SUMMARY OF RELEVANT PREVIOUS FDA SAFETY REVIEWS

The Division of Pharmacovigilance (DPV) performed a review evaluating the risk of developing serotonin syndrome with the 5-HT₃ receptor antagonist drug class on February 13, 2013.² The review included 39 cases of serotonin syndrome with ondansetron (n=29), granisetron (n=7), dolasetron (n=2), and ondansetron and granisetron in combination (n=1) identified in the FDA Adverse Event Reporting System (FAERS) database and medical literature. There were no cases found for palonosetron. Most cases involved use of a concomitant serotonergic agent, although there were two cases related to accidental overdoses of ondansetron as a single agent. There were three deaths, of which two were related to serotonin syndrome. Analysis of the cases revealed potential for developing serotonin syndrome with the 5-HT₃ receptor antagonist drug class when used alone or concomitantly with other serotonergic drugs in all age groups. The recommendation was to include serotonin syndrome in the label for all 5-HT₃ receptor antagonists.

DPV performed a review evaluating all reported serious adverse events including QT prolongation with palonosetron on June 23, 2016.³ (b) (4)

NDA 21372 Aloxi (palonosetron hydrochloride) injection, (b) (4)
A search of FAERS from January 1, 2014 to June 9, 2016 retrieved 385 adverse event reports with a serious outcome associated with the use of palonosetron. A high level overview of the 385 reports revealed the majority of adverse events were labeled, indication-related, or related to the patient's underlying disease. There were 47 death cases, of which 16 were duplicates and 31 had a strong alternative cause or provided limited information to determine causality. Eight cases reported Torsades de Pointes or QT prolongation, of which two were duplicate and six were unique cases; all six unique cases contained concomitant medications labeled for QT prolongation. DPV did not identify any new serious safety signals.

On May 5, 2014, as part of the clinical review for sNDA 21372/S-018 and S-019, two DGIEP medical officers reviewed postmarketing safety data in pediatrics and data not represented in the labeling in adults for the period of July 25, 2003 to September 30, 2013.^{4,5} This postmarketing data was submitted in response to the pediatric WR for palonosetron. Four adverse event reports with non-serious outcomes occurring in pediatric patients 7 to 17 years of age receiving palonosetron for CINV were reviewed. Three reports contained “listed” adverse events; two reported lack of efficacy and one reported inappropriate dosing of palonosetron with no associated adverse event. One contained “unlisted” adverse events of hyponatremia, muscle spasm, and tremor, but occurred in a patient receiving concomitant thiotepa and furosemide. The medical officers concluded that the four reports did not appear to present any new safety signals with palonosetron injection in the pediatric population.

1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES

1.4.1 Palonosetron

The palonosetron labeling dated September 2014 contains the following safety highlights:¹

-----CONTRAINDICATIONS-----

- ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components. [*see Adverse Reactions (6.2)*]

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

- *Hypersensitivity* Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT₃ receptor antagonists (5.1).
- *Serotonin Syndrome* The development of serotonin syndrome has been reported with 5-HT₃ receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT₃ receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT₃ receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Aloxi and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Aloxi and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Aloxi is used concomitantly with other serotonergic drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

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

- Chemotherapy-Induced Nausea and Vomiting (6.1)

Pediatrics: In a pediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting 163 cancer patients received a single 20 mcg/kg (maximum 1.5 mg) intravenous infusion of palonosetron 30 minutes before beginning the first cycle of emetogenic chemotherapy. Patients had a mean age of 8.4 years (range 2 months to 16.9 years) and were 46% male; and 93% white.

The following adverse reactions were reported for palonosetron:

Nervous System: <1%: headache, dizziness, dyskinesia.

General: <1%: infusion site pain.

Dermatological: <1%: allergic dermatitis, skin disorder.

In the trial, adverse reactions were evaluated in pediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

- Postmarketing Experience (6.3)

The following adverse reactions have been identified during postapproval use of ALOXI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Very rare cases (<1/10,000) of hypersensitivity reactions including anaphylaxis and anaphylactic shock and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience of ALOXI 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

-----**DRUG INTERACTIONS**-----

- Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.
- Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) [*see Warnings and Precautions (5.2)*].

-----**USE IN SPECIFIC POPULATIONS**-----

- *Pediatric Use* Safety and effectiveness of ALOXI have been established in pediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Use is supported by a clinical trial where 165 pediatric patients aged 2 months to <17 years were randomized to receive a single dose of palonosetron 20 mcg/kg (maximum 1.5 mg) administered as an intravenous infusion 30 minutes prior to the start of emetogenic chemotherapy [*see Clinical Studies (14.2)*]. While this study demonstrated that pediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults [*see Adverse Reactions (6.1)*].

Safety and effectiveness of ALOXI in neonates (less than 1 month of age) have not been established (8.4).

-----**CLINICAL PHARMACOLOGY**-----

- *Pharmacodynamics* The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg (12.2).

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. The time periods examined in each data source were dependent upon data availability. Detailed descriptions and limitations of the databases are included in Appendix A.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for palonosetron from June 2014 through November 2016, cumulative. Sales data for palonosetron by the number of vials sold from the manufacturer to all U.S. channels of distribution indicated that approximately 99.5% of vials were sold to non-retail pharmacies (mainly clinics) and 0.5% of vials were sold to retail/mail-order/specialty pharmacy settings.⁶ Palonosetron is a 5-HT₃ receptor

antagonist administered by a healthcare provider. Therefore, this drug utilization analysis focuses on palonosetron use based on outpatient prescription and/or medical claims data from a sample of pharmacies, hospitals and clinics.

2.1.2 Data Sources Used

The Symphony Health Solutions' Integrated Dataverse (IDV)TM database was used to obtain the number of unique patients with the pharmacy prescription/medical claim for palonosetron injection, stratified by patient age (0-1 year, 2-16 years, and 17+ years), from June 2014 through November 2016, cumulative. National projections of this data are not available and thus the data only represent a sample of 198 pharmacies, 3,100 clinics, hospitals and physician offices.

Patient selection in Symphony Health Solutions' IDV database was based on the presence of a pharmacy prescription claim using National Drug Code for palonosetron injection and/or the presence of a medical claim using the Health Care Common Procedure Coding System (HCPS code J2469) which represents administration of palonosetron by a health care provider.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1

	Jun 2014 - Nov 2016	
	Patient Count	Share
	N	%
Grand Total	322,149	100.0%
Age 0 - 16 yrs	236	0.1%
0 - 1 yr	15	6.4%
2 - 16 yrs	221	93.6%
Age 17+ yrs	321,906	99.9%
Unknown Age	7	0.0%

Source: Symphony Health Solutions' Integrated Dataverse (IDV). June 2014 - November 2016. Extracted March 2017. File: SHSIDV 2016-2411 Aloxi patient counts by age 3-6-17.xls

** Age is at first claim during examined time.*

Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months old).

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	December 15, 2016
Time Period of Search	July 25, 2003* - December 1, 2016
Search Type	Product-Manufacturer Reporting Summary
Product Active Ingredient	Palonosetron, palonosetron hydrochloride†
Search Parameters	All ages, all outcomes, worldwide

* July 25, 2003 was the date of initial approval of palonosetron; this date will capture all reports of off-label use of palonosetron in pediatric patients and all reports occurring after the pediatric labeling date of May 27, 2014.

† The search strategy used *Product Active Ingredient* palonosetron and palonosetron hydrochloride, which would retrieve adverse event reports with all palonosetron formulations (injection, oral soft capsule).

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* July 25, 2003 to December 1, 2016 with palonosetron or palonosetron hydrochloride

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	473 (226)	358 (113)	40 (18)
Pediatrics (0 - <17 years)	11‡ (1)	10 (0)	0 (0)

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

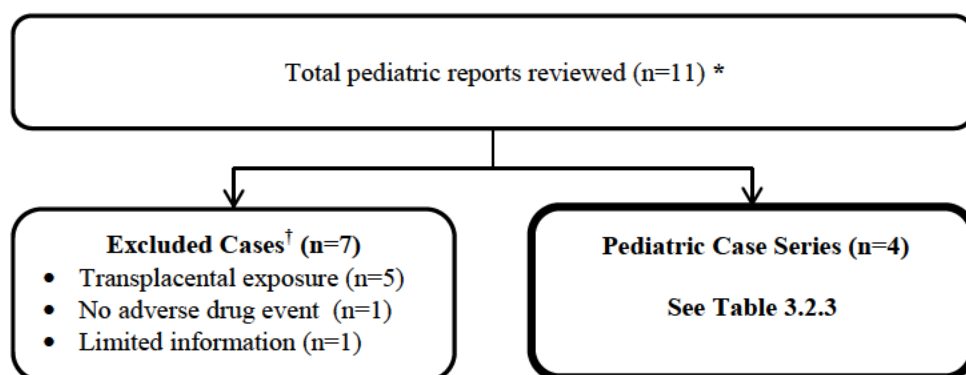
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

3.2.2 Selection of Pediatric Cases in FAERS

We identified 11 pediatric reports with palonosetron injection, of which 10 had a serious outcome and one had a non-serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Pediatric Cases in FAERS with Palonosetron Injection



* All pediatric reports involved palonosetron injection. There were no pediatric reports with the outcome of death.

† DPV-I reviewed these cases, but they were excluded from the case series for the reasons listed above.

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of FAERS Pediatric Case Series with Palonosetron Injection (N=4)

Age	6- <12 years	3
	12- <17 years	1
Sex	Male	2
	Female	2
Country	Foreign	4
Reported Reason for Use	CINV	4
Serious Outcome*	Hospitalized	1
	Other serious	4
Initial Year Received	2014	4

* 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. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no fatal pediatric adverse event cases included in this case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

Nervous System Disorders (n=1)

Unlabeled Event: Extrapyramidal symptoms (n=1)

Case 10521824, outcome- other serious important medical event, Spain, 2014: A physician reported that an 8-year-old male with sclerosing rhabdomyosarcoma experienced extrapyramidal symptoms described as “twitching and dystonia in muscles of lower limbs and neck” three days after receiving the second cycle of palonosetron hydrochloride. Ifosfamide, vincristine, and doxorubicin were administered on two consecutive days starting the same day of palonosetron administration. Other concomitant medications included actinomycin, metamizol, pethidine hydrochloride, and paracetamol. Palonosetron was discontinued and the physician “distrusted” the antiemetic. The patient was reported to have “good tolerance to Akineton (biperiden)” and the event resolved three days later with repeated administration.

*Reviewer’s comment: Extrapyramidal symptoms are an unlabeled adverse event for palonosetron, but are labeled for another 5-HT₃ receptor antagonist, ondansetron.⁷ Because this was identified with another drug in the same class, we performed an additional FAERS search in the **adult** population to identify any additional cases of extrapyramidal symptoms with palonosetron. A single foreign case in a 50-year-old female was identified; however, the case contained limited information to properly assess causality (see Appendix D for FAERS search strategy and results).*

Ifosfamide was administered for two consecutive days starting the same day as palonosetron. The ifosfamide label contains a Boxed Warning for Central Nervous System (CNS) toxicities and is labeled for CNS toxicities including extrapyramidal symptoms in Warnings and Precautions Section 5.2 and Adverse Reactions Section 6.1.⁸ The product labeling for ifosfamide states that neurotoxicity may manifest a few hours to a few days after the first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. The time to onset and resolution of ifosfamide-associated neurotoxicity are similar to the timeframe described in this case. Therefore, ifosfamide-associated CNS toxicity is a strong alternative cause of the extrapyramidal symptoms.

Serotonin syndrome is listed in Warnings and Precautions Section 5.2 of the palonosetron product label. Serotonin Syndrome may include neuromuscular symptoms that resemble extrapyramidal symptoms, such as tremor, rigidity, myoclonus, hyperreflexia, and incoordination. This patient received concomitant pethidine hydrochloride, also known as meperidine. Meperidine blocks the neuronal reuptake of serotonin and can cause serotonin syndrome in combination with other medications such as monoamine oxidase inhibitors.⁹ Another alternative explanation is that this patient experienced serotonin syndrome from the combination of palonosetron and pethidine. The patient was noted to respond to anticholinergic treatment (biperiden) which makes this explanation less likely.

Immune System Disorders (n=3)

Labeled Event: Hypersensitivity (n=3)

“Hypersensitivity reactions, including anaphylaxis” are labeled in the Warnings and Precautions Section 5.1 and Postmarketing Experience Section 6.3 of the palonosetron product label.

The following three cases were all submitted by the same reporter:

Case 10255357, outcome- other serious important medical event, Mexico, 2014: A physician reported that an 11-year-old female experienced diaphoresis, shortness of breath, and tachycardia sometime after receiving intravenous Onicit (palonosetron) 0.25 mg for prophylaxis of CINV. The patient had been receiving palonosetron for approximately 7 months prior to the adverse event. Concomitant medications administered on the same day as palonosetron included intramuscular methotrexate 46 mg and intravenous cytarabine 350 mg administered over 3 hours for treatment of acute lymphocytic leukemia. Palonosetron was discontinued and the outcome of the event was reported as recovered (date not provided). The reporter considered the patient's symptoms to be a hypersensitivity reaction to palonosetron.

Case 10255364, outcome- hospitalization/other serious important medical event, Mexico, 2014: A physician reported that an 11-year-old male experienced diaphoresis, shortness of breath, anxiety, vomiting, and tachycardia after receiving Onicit (palonosetron) 0.25 mg intravenously for prophylaxis of CINV. The patient was hospitalized for hydration, control of electrolytes, and vital sign monitoring. The patient had been receiving palonosetron for approximately 7 months prior to the adverse event. Concomitant medications included intravenous etoposide 350 mg administered over 4 hours and intravenous cytarabine 350 mg administered over 3 hours weekly for treatment of acute lymphocytic leukemia. Palonosetron was discontinued and the outcome of the adverse events of diaphoresis, shortness of breath, and tachycardia was reported as recovered.

Case 10255590, outcome- other serious important medical event, Mexico, 2014: A physician reported that a 16-year-old female experienced diaphoresis, tachycardia, shortness of breath, anxiety, and crying after administration of Onicit (palonosetron hydrochloride). The patient had been receiving palonosetron 0.5 mg intravenously weekly for approximately 16 months prior to the event. Concomitant medications administered on the same day as palonosetron included intramuscular methotrexate 59 mg and intravenous cytarabine 440 mg infused over 3 hours for treatment of acute lymphocytic leukemia. Palonosetron was discontinued and the events of diaphoresis, tachycardia, and shortness of breath were reported as recovered.

Reviewer's comment: The reporter did not provide the time of onset of the adverse events relative to palonosetron and concomitant chemotherapy medication administration. In all three cases, the patients had been receiving palonosetron for multiple months prior to the onset of the events; however, it is unclear how long they were receiving the specific chemotherapy medications. The constellation of symptoms described in the reports may represent a hypersensitivity reaction; however, we cannot attribute the adverse events to

a single medication because of limited information. Hypersensitivity reactions are already included in the palonosetron product label.

4 DISCUSSION

Our drug utilization analysis showed that the pediatric population accounted for approximately 0.1% (236 patients) of total patients with a prescription and/or medical claim for palonosetron in our study sample that spanned the time period from June 2014 through November 2016. Approximately 94% of pediatric patients were aged 2-16 years (221 patients) and 6% of pediatric patients were aged 0-1 year (15 patients). Although the data on patient utilization were obtained from a robust sample of outpatient pharmacies and clinics, the data may not be representative of overall national use or use in other settings of care not captured such as inpatient utilization.

We evaluated all FAERS reports of adverse events in the pediatric population for palonosetron from the initial FDA approval of palonosetron injection in adults on July 25, 2003 to December 1, 2016. The initial approval date was used to capture all reports of off-label use of palonosetron in pediatric patients and all reports occurring after the pediatric labeling date of May 27, 2014. The review of FAERS pediatric reports resulted in identification of four non-fatal cases with a serious outcome. No new safety signals were identified after review of the four cases. Of the four cases, one reported an unlabeled event of extrapyramidal symptoms and three reported a labeled event of hypersensitivity reaction with an additional constellation of symptoms such as dyspnea, diaphoresis, and tachycardia. The single pediatric case of extrapyramidal symptoms did report a temporal association to palonosetron administration; however, the patient was receiving concomitant ifosfamide. Ifosfamide is labeled for CNS toxicity including extrapyramidal symptoms. The time to onset and resolution of ifosfamide-associated neurotoxicity described in the ifosfamide product label is similar to the timeframe reported in the single pediatric case. The three remaining cases of hypersensitivity reactions described patients who received concomitant chemotherapy agents and because of limited information, it is not possible to attribute the reaction to palonosetron alone. Hypersensitivity reactions are labeled for palonosetron and at this time no additional changes to the label are recommended.

5 CONCLUSION

The Office of Surveillance and Epidemiology analyzed the following data: 1) pediatric drug utilization data for Aloxi (palonosetron) injection and 2) the pediatric postmarketing adverse event reports for palonosetron received in FAERS from July 25, 2003 to December 1, 2016. There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

DPV plans to continue routine postmarketing surveillance of all adverse events with the use of palonosetron in pediatric patients.

7 APPENDICES

7.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that palonosetron was distributed primarily to the non-retail setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Symphony Health Solutions' IDV® (Integrated Dataverse)

Symphony Health Solutions' IDV (Integrated Dataverse) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Data from Symphony Health Solutions' Integrated Dataverse (IDV) provides unprojected patient counts with a prescription and/or medical claim for palonosetron. Due to the sample size and the unreported pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of clinics contributing to these data are unknown, therefore, nationwide projections are not available at this time.

7.2 APPENDIX B. FAERS

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=4)

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
10255357	3	2014MX010480
10255364	2	2014MX010479
10255590	3	2014MX010481
10521824	3	2014ES010650

7.4 APPENDIX D. ADDITIONAL FAERS SEARCH STRATEGY AND RESULTS

Table 8.4.1 FAERS Search Strategy

Date of Search	January 19, 2017
Time Period of Search	No date restrictions
Search Type	Quick Query
Product Active Ingredient	Palonosetron, palonosetron hydrochloride [†]
MedDRA Search Term (Version 19.0)	Preferred Term <i>Extrapyramidal disorder</i>

The FAERS search retrieved one adverse event report of extrapyramidal disorder occurring in an adult patient, which is described below.

Case #10305387, other serious important medical event, Thailand, 2014: A physician reported that a 50-year-old female experienced an “extrapyramidal effect for neck contraction” after receiving concomitant aprepitant, dexamethasone, palonosetron (indication for use was CINV), and unknown antipsychotic medication. The event was not a seizure or convulsion. Aprepitant, palonosetron, and dexamethasone were discontinued and the patient received benztropine for treatment. The event resolved. The physician thought the event might be related to aprepitant or the antipsychotic medication.

Reviewer’s comment: The physician attributed the event to aprepitant or the antipsychotic medication; however, there is insufficient information in the case to determine the actual causal medication. Like palonosetron, aprepitant is not labeled for extrapyramidal symptoms and the information provided in the case does not confirm an association between the extrapyramidal symptoms and aprepitant.¹⁰ First and second generation antipsychotic medications can produce extrapyramidal symptoms with varying frequencies, but we cannot attribute the extrapyramidal symptoms to the antipsychotic medication because of lacking information.¹¹

8 REFERENCES

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- ⁷ Zofran (ondansetron) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; Label revised October 2016.
- ⁸ Ifosfamide [package insert]. Deerfield, Illinois: Baxter Healthcare Corporation; Label revised August 2014.
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- ¹⁰ Emend (aprepitant) [package insert]. Whitehouse Station, New Jersey: Merck & Co.; Label revised January 2017.
- ¹¹ Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician* 2010;81:617-22.

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