DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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MEMORANDUM TO FILE

Pediatric and Maternal Health Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health Miriam Dinatale, D.O., Medical Officer, Maternal Health Division of Pediatric and Maternal Health
Through:	Hari Cheryl Sachs, MD Team Leader Division of Pediatric and Maternal Health Tamara Johnson, MD, MS, Team Leader, Maternal Health Division of Pediatric and Maternal Health John J. Alexander, MD, MPH Acting Deputy Director Division of Pediatric and Maternal Health
NDA Number:	207-963
Sponsor:	Exela Pharma Sciences
Drug:	Palonosetron Injection
Dosage form and route of administration:	injection for intravenous use
Proposed indications:	Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

Consult request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests assistance from the Division of Pediatric and Maternal Health (DPMH) as they review this 505(b)(2) NDA, including labeling.

Background

The sponsor originally submitted this 505(b)(2) NDA relying on the findings of safety and efficacy of Aloxi® (palonosetron HCl) NDA 21-372 on August 7, 2014. The application received a Complete Response on June 15, 2015. The sponsor submitted a resubmission on September 22, 2015. The application does not trigger PREA.

The innovator, Aloxi®, received pediatric exclusivity on April 10, 2014 and was approved for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy in pediatric patients aged 1 month to less than 17 years on May 27, 2014. Of note, an assessment of Aloxi® f (b) (4) Thus, Aloxi has the following indications:

Aloxi® is a serotonin-3 (5-HT3) receptor antagonist indicated in adults for:

- Moderately emetogenic cancer chemotherapy --prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy --prevention of acute nausea and vomiting associated with initial and repeat courses
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

Aloxi® is indicated in pediatric patients aged 1 month to less than 17 years for:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy

Hypotonicity of the product

This product has a tonicity of approximately 0 mOSM/kg. Safety concerns including injection site pain and hemolysis were raised because of the hypotonicity of the formulation. The sponsor conducted a local irritation study which confirmed that this product does not present a safety concern related to local irritation. The sponsor also conducted an *in vitro* hemolysis study which does not suggest that the hypotonic solution of the 2 mL adult dose will result in clinically relevant hemolysis. The highest concentration tested was a 1:10 dilution which did not demonstrate significant hemolysis.

Concern was raised that the hypotonicity of the formulation may cause a safety concern in pediatric patients if this product is used off-label in pediatric patients. However, calculations of potential dosing based on the recommended dosing in the Aloxi labeling show that the dilution in the average blood volume for weight was approximately 1:500. The following chart was developed by Dr. Aisha Johnson, a clinical reviewer in DGIEP. See Dr. Johnson's review for additional information.

Pediatric Dose/Volume Estimates and Calculated TBV Dilution[1]

Age	Weight*	Dose‡ (20 mcg/kg)	Drug Volume§ (0.125 mg/mL)	Average Total Blood Volume# (mL)	Dilution†
1 month	4.4 kg	0.088 mg	0.7 mL	350	1:500
6 months	6.4 kg	0.13 mg	1 mL	500	1:500
9 months	7.4 kg	0.14 mg	1.1 mL	600	1:545
6 years	16 kg	0.32 mg	2.6 mL	1120	1:430
10 years	26 kg	0. 52 mg	4.2 mL	1820	1:433
16 years	50 kg	1.0 mg	8.0 mL	3500	1:437
		MAX DOSE 1.5 mg	**MAX VOLUME** 12 mL		

Reviewer's Table.
*Weight based on CDC growth charts, 5th percentile average of boys and girls
#Total Blood Volume estimated using approximation to Nadler's equation (80 mL/kg until 1 year, then 70 mL/kg)
‡Dose (in mg) calculated as Weight X .020 mg/kg
§Drug volume (in mL) calculated as follows: Dose (in mg) / 0.125 mg/mL

1 http://www.cdc.gov/growthcharts/data/who/grchrt_boys_24lw_100611.pdf and http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf

Reviewer comment: The 1:500 dilution compared to the 1:10 dilution in the in vitro *study provides reassurance that significant hemolysis should not occur if this product is administered to pediatric patients.*

Discussion and Recommendations

The indication sections of the Highlights section appropriately expresses that the indication is approved in adults only for this product. The indication section in the Full Prescribing Information should express that the indication is approved in adults only for this product as well.

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. 21 CFR 201.57(c)(9)(iv) describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population and allows an alternative statement to be included if the required statement is not appropriate.

Pregnancy and Lactation Labeling Recommendations

In April 2015 and January 2016, DPMH conducted a review of published literature regarding palonosetron and pregnancy, lactation and females and males of reproductive potential, and provided labeling recommendations for this application to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The reader is referred to the DPMH reviews by M. Dinatale, D.O., for further details.[1,2] Previous labeling recommendations,

[1] DPMH review of palonosetron Hydrochloride (NDA 207963). Miriam Dinatale, DO. April 29, 2015. DARRTS Reference ID 3741833

that were not applied due to issuance of the Complete Response, are now being implemented in the current palonosetron labeling. No new labeling recommendations are provided at this time.

Sponsor Proposed Pediatric Labeling and DPMH Recommended Labeling

1 INDICATIONS AND USAGE

1.1 Chemotherapy-Induced Nausea and Vomiting

Palonosetron Injection is indicated in adults for:

- Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses

- Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

8.4 Pediatric Use

(b) (4)

This product has not been approved for use in pediatric patients for prevention of chemotherapy-induced nausea and vomiting.

Rationale

Safety and effectiveness of the Aloxi® formulation of palonosetron has been demonstrated 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. Information on pediatric dosing, safety, pharmacokinetics, and a description of the pediatric studies supporting pediatric use is protected by the exclusivity awarded to the innovator Aloxi®. Therefore, this information cannot be included in labeling for this 505(b)(2) product. Including a statement that safety and effectiveness have not been established for pediatric patients for the CINV indication would not be a true statement. Safety and effectiveness have been established for pediatric CINV in Aloxi® (b) (4) tating that "this product has not been approved for pediatric use" is a true statement and is an alternative statement as allowed under the regulations. DPMH recommends using the more general indication of "chemotherapy-induced nausea and vomiting" in order to avoid the possibility of including protected information in the labeling. (b) (4)

[2] DPMH review of palonosetron Hydrochloride (NDA 203050). Miriam Dinatale, DO. January 25, 2016. DARRTS Reference ID 3875380

Additional comments:

The hypotonicity of this product does not represent a safety concern if the product is administered off-label in pediatric patients.

These recommendations were communicated to DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

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/s/

AMY M TAYLOR
03/02/2016

MIRIAM C DINATALE
03/02/2016

HARI C SACHS
03/02/2016
I agree with these recommendations.

TAMARA N JOHNSON
03/02/2016

JOHN J ALEXANDER
03/02/2016