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APPLICATION NUMBER:

207963Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207,963
Priority or Standard	Standard
Submit Date(s)	September 23, 2015
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PDUFA Goal Date	March 22, 2016
Division / Office	DGIEP/ODE 3
Reviewer Name(s)	Aisha Peterson Johnson, MD, MPH, MBA
Review Completion Date	25 February 2016
Established Name	Palonosetron hydrochloride
(Proposed) Trade Name	Palonosetron Injection
Therapeutic Class	5-HT_3 antagonist
Applicant	Exela Pharma Sciences
Formulation(s)	Solution for Intravenous Injection, 0.125 mg/mL
Dosing Regimen	CINV: 0.25 (b) (4) mg IV dose administered over 30 seconds approximately 30 minutes before the start of chemotherapy.
Indication(s)	Chemotherapy-induced Nausea and Vomiting - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the current submission, the Applicant is proposing the following indication for Palonosetron Injection (NDA 207,963) in adults:
Chemotherapy-Induced Nausea and Vomiting

- 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

In the first review cycle for this NDA, the Applicant, Exela Pharma Sciences (b) (4)

After reviewing the Applicant's current Complete Response submission, this reviewer recommends the approval of Palonosetron Injection (NDA 207,963) for the proposed indication if no other discipline has deficiencies that preclude approval and the following issues are resolved:

1. The biowaiver for the in vivo BA/BE study is granted (Section 2.1)
2. The Product Quality deficiency is adequately addressed (Section 4.2)
3. DMEPA's recommendations regarding changes to the carton and container labeling are implemented by the Applicant (Section 7.3.5)

1.2 Risk Benefit Assessment

Palonosetron hydrochloride for injection has been available in the US market since 2003 as ALOXI. During this time, no significant safety changes have been made to the product label. The drug contains no boxed warnings and patients receive just one dose per chemotherapy cycle to prevent nausea and vomiting. The Applicant submitted a 505(b)(2) application relying on the Agency's finding of safety and efficacy of ALOXI Injection (NDA 21372, Helsinn Healthcare SA).

The proposed new formulation provides the equivalent amount of the active ingredient as ALOXI injection, the reference drug, for the prevention of CINV. However, the concentration of palonosetron hydrochloride is higher in the proposed product (0.125 mg/mL) compared to Aloxi (0.05 mg/mL). Further, the proposed formulation does not contain disodium edetate (b) (4) citrate (b) (4) or mannitol (b) (4)

(b) (4). The product has a tonicity of approximately 0 mOSM/kg (compared with 300 mOSM/kg, Aloxi). Safety concerns of a hypotonic intravenous solution include injection site pain and hemolysis. Results of a local irritation study conducted in the first review cycle confirmed that this product does not present a safety concern related to local irritation. Similarly, the analysis of the results of the *in vitro* hemolysis study submitted in the current review cycle do not suggest that the hypotonic solution of the 2mL adult dose will result in clinically relevant hemolysis.

The reference drug, ALOXI, is known to be efficacious for the prevention of CINV and relatively safe. Despite the hypotonicity of the proposed Palonosetron Injection product, the results of safety studies (local irritation and hemolysis) support the safety of the formulation. Therefore, the known benefits of the proposed unbuffered, hypotonic, preservative-free Palonosetron Injection product outweigh the known risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and/or commitments are recommended. Palonosetron Injection does not contain a new active ingredient, new indication(s), new dosage form(s), new dosing regimen(s), or new route(s) of administration compared to ALOXI, the reference drug. Therefore, as per the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the sponsor is not required to evaluate the use of Palonosetron Hydrochloride injection in the pediatric population for the same indications as adults.

2 Introduction and Regulatory Background

2.1 Product Information

Palonosetron Hydrochloride Injection is a 5-HT3 receptor antagonist. It is an antiemetic/antinauseant drug. NDA 207,963 for Palonosetron Hydrochloride Injection, 0.125mg/mL refers to the listed drug, ALOXI® (Palonosetron Hydrochloride) Injection, 0.075mg/1.5mL and 0.25mg/5mL (NDA 21372) published in Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

The proposed palonosetron formulation is intended to be therapeutically equivalent to ALOXI. Pursuant to 21 CFR §320.22(b)(1), the Sponsor requested a biowaiver for the bioavailability/ bioequivalence (BA/BE) requirement.

In the Complete Response Letter, the Applicant was notified that their request for a biowaiver could not be granted until the safety issues related to the hypotonicity of the proposed product are resolved.

MO Comment:
In the opinion of this reviewer, the safety issues related to the hypotonicity of the proposed product have been adequately addressed. Therefore, these issues should no longer preclude granting of the biowaver. See Section 7 for a full discussion of the safety issues related to the hypotonicity of the proposed product.

Table 1. Formulation Differences

	Aloxi	Palonosetron HCl
Concentration	0.05 mg/mL	O.125 mg/mL
CINV Adult dose and volume	0.25 mg (5 mL)	0.25 mg (2 mL)
CINV Pediatric dose	20 mcg/kg (max 1.5mg)	N/A
PONV Adult dose and volume	0.075 mg (1.5 mL)	N/A
Excipients	Mannitol (b) (4) Disodium edetate (b) (4) Citrate (b) (4)	NOT PRESENT
Tonicity	300 mOSM/kg	~0 mOSM/kg

Reviewer's Table.

The Applicant expects that because their proposed IV palonosetron product is administered as an injectable solution, there should be no difference in the systemic exposure, safety, or efficacy of their product compared with the reference drug, ALOXI. The Sponsor's formulation is intended to be administered as an IV solution of the same dose and dosing regimen as that of the reference drug.

With their initial NDA submission, the Applicant submitted a Paragraph III certification [per 21 CFR 314.50(i)(1)(i)(A)(3)] for patent 5202333. This patent expired during the initial review cycle on April 13, 2015 with pediatric exclusivity expiring during the current review cycle on October 13, 2015.

The Applicant submitted Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] against the other patents listed for ALOXI in the Orange Book noting that these patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the Applicant's proposed Palonosetron Injection.

ALOXI, the reference drug, has pediatric exclusivity which expires in 2017.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2. Summary of Approved Pharmacotherapies for Nausea and Vomiting

Drug	Dosage Form	Indications					
		PONV		CINV		Other NV	
		Prevention	Treatment	Prevention		Prevention	Treatment
				HEC	MEC		
5-HT3 Receptor Antagonists							
Zofran (ondansetron)	IV	√		√*	√*		
	Oral	√		√	√*	Radio-therapy	
Anzemet (dolasetron)	IV	√	√				
	Oral				√*		
Kytril (granisetron)	IV	√	√	√*	√*		
	Oral	√	√	√*	√*		
Sancuso (granisetron)	Trans-dermal			√	√		
Aloxi (palonosetron)	IV	√	√	√*,†	√*,#		
	Oral				√*,#		
NK1 Receptor Antagonists							
Emend (aprepitant)	Oral	√		√*,#	√* Non-specific regarding acute and delayed		
Emend (fosaprepitant) 3-day IV/oral/oral	IV			√*,#	√* Non-specific regarding acute and delayed		
Emend (fosaprepitant) Single dose	IV			√*,#	√*,# Delayed only		
Varubi (rolapitant)	Oral			√*,# Delayed only	√*,# Delayed only		
5-HT3 and NK-1 Antagonist							
Akynzeo (palonosetron and netupitant)	Oral			√*,#	√*,#		
H1 Receptor Antagonists							
Antivert (meclizine)	Oral					Motion Sickness	Motion Sickness

Anticholinergics							
Transderm Scop (scopolamine)	Trans-dermal	√				Motion Sickness	
Other							
Tigan (trimtho-benzamide HCl)	IM		√				Gastro-enteritis
	Oral		√				Gastro-enteritis

CINV: Chemotherapy-Induced Nausea and Vomiting
PONV: Post-operative Nausea and Vomiting
NV: Nausea and Vomiting
HEC: Highly Emetogenic Chemotherapy
MEC: Moderately Emetogenic Chemotherapy
*initial and repeat courses
#acute and delayed
†acute
Source: Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)
Table created by Anil Rajpal, MD, MPH

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, palonosetron, was first approved on July 25, 2003 in ALOXI ® Injection. Palonosetron is currently marketed in the US as the ALOXI® brand. Palonosetron hydrochloride is available in injectable form for intravenous administration.

In this NDA application, the Applicant submits Palonosetron Injection as an alternative formulation to the referenced ALOXI injection product.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety Issues included in current ALOXI labeling include:

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other selective 5-HT3 receptor antagonists (Section 5.1)
- Serotonin syndrome has been reported with 5-HT3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs (Section 5.2)
- Cardiac arrythmias

The use of the 5-HT3 receptor antagonist class has been associated with cardiac arrhythmias. These events have been seen primarily in patients receiving the intravenous forms of these drugs. The ALOXI sponsor conducted and submitted a thorough QT trial in 2007. No significant effect of palonosetron administration on any ECG interval including QTc duration at doses up to 2.25 mg was seen in this trial. The ALOXI label was updated to include this information.

In December 2010, the FDA contraindicated the use of dolasetron I.V. in adults and children for the prevention of CINV due to serious cardiac arrhythmias, i.e. prolonged

QTc interval. On June 29, 2012, the FDA issued a drug safety communication for Ondansetron (Zofran) I.V. related to QT prolongation observed at the 32 mg single I.V. administered dose.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For regulatory activities prior to the first cycle submission, see the clinical review by Dr. Laurie Muldowney (DARRTS 15 June 2015).

On 07 August 2014, the Applicant submitted the original NDA to the FDA for review. On 15 June 2015, the FDA issued a Complete Response Letter (CRL) to the Applicant. On September 23, 2015, the Applicant their formal response to the deficiencies outlined in the CRL. It is this submission that is the subject of the current review.

2.6 Other Relevant Background Information

There is no other relevant background information, except as discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of this submission was good. The application was electronic, non-ECTD format with an adequate layout which made substantive review straightforward.

3.2 Compliance with Good Clinical Practices

N/A
No clinical trials were conducted for this 505(b)(2) application.

3.3 Financial Disclosures

N/A
No clinical trials were conducted for this 505(b)(2) application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The hypotonicity of the proposed drug product is discussed in Section 7.

4.2 Clinical Microbiology

During the first review cycle, the Product Quality Microbiology reviewer identified one deficiency.

Product Quality Deficiency #1 (from the CRL)
You have not provided an adequate description of the holding times associated with the processing of the finished drug product. Provide the (b) (4) for the drug product

Discussion of Applicant's response to Product Quality Deficiency Item #1
The Applicant stated that they would execute a formal bulk (b) (4) study as part of the prospective process performance qualification for the drug product.

For a discussion regarding the adequacy of these study results to address the deficiency, please see the second cycle Product Quality Microbiology review in DARRTS.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical/toxicology studies were submitted during the first or current review cycles. The Applicant did submit an I hemolysis study that was reviewed by the pharmacology/toxicology reviewer. The results of the hemolysis study are discussed in Section 7 of this review. For a full discussion of the hemolysis study results, see the review by Tracy Behrsing, PhD in DARRTS.

4.4 Clinical Pharmacology

During the first review cycle, NDA 207963 was found to be acceptable from the Clinical Pharmacology perspective.

No additional clinical pharmacology data was submitted for review during the current review cycle.

4.4.1 Mechanism of Action

As per the ALOXI label

4.4.2 Pharmacodynamics

As per the ALOXI label

4.4.3 Pharmacokinetics

As per the ALOXI label

5 Sources of Clinical Data

No clinical trials were submitted to support the efficacy of the proposed product. However, the Applicant did conduct and submit for review a local irritation study (submitted during the first review cycle) and a hemolysis study (submitted during the current review cycle) to support the safety of the proposed product.

5.1 Tables of Studies/Clinical Trials

As described above.

5.2 Review Strategy

Conclusions regarding the hemolysis study are presented in Section 7. For a full review of the hemolysis study see the nonclinical review by Tracy Behrsing, PhD.

5.3 Discussion of Individual Studies/Clinical Trials

N/A

6 Review of Efficacy

Efficacy Summary

The proposed product is relying upon the Agency's findings of safety and efficacy of ALOXI.

6.1 Indication

Chemotherapy-Induced Nausea and Vomiting

- 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

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

No new safety data was submitted using the proposed drug product. The Applicant submitted a postmarket safety update of ALOXI. No new safety signals were identified upon review of the post market data.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See description of included trials in Section 7.1.

7.1.2 Categorization of Adverse Events

N/A

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

N/A

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

N/A

7.3.1 Deaths

N/A

7.3.2 Nonfatal Serious Adverse Events

N/A

7.3.3 Dropouts and/or Discontinuations

N/A

7.3.4 Significant Adverse Events

N/A

7.3.5 Submission Specific Primary Safety Concerns

The Complete Response Letter (CRL) outlined two clinical safety deficiencies. In the current submission, the Applicant addressed both of these deficiencies.

Clinical Deficiency #1 (from the CRL)
You did not provide sufficient information to establish the safety of the proposed formulation of your drug product. You have not established that the hypotonicity of your drug product will not result in clinically relevant hemolysis.

To address this deficiency, data can be provided from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. Particularly address the potential for hemolysis in patients with smaller blood volumes in whom the potential for hemolysis may be greater.

In addition, provide justification that the design (including sample size and choice of comparator) and results of Study EPS-2014-001 support that the tonicity and pH will not pose a significant safety risk.

Discussion of Applicant's response to Clinical Deficiency Item #1

To address the potential for the hypotonic drug product to produce clinically relevant hemolysis, the Applicant conducted a hemolysis study. The hemolysis study evaluated all four NDA submission stability lots of Palonosetron Injection, 0.125 mg/mL. Eight concentrations of the drug product in blood were evaluated ranging from 0.098 mcg/mL

to 12.5 mcg/mL. The highest concentration represented a 10% dilution in blood (chosen to address the potential for hemolysis in patients with smaller blood volumes). Based on the study results, the Applicant concluded that any hemolysis observed for the test articles at any concentration in any of the four different lots was similar to vehicle control. The FDA pharmacology reviewer, Tracy Behrsing, PhD, agreed with that conclusion. See the complete pharmacology/toxicology review in DARRTS.

The highest concentration tested in the hemolysis study represented a 10% dilution. Given that Aloxi, the reference drug, has a pediatric indication, it is important to address the potential for off-label use of palonosetron hydrochloride in pediatric patients. To address this concern, the ratio of palonosetron hydrochloride drug volume to total blood volume (TBV) of pediatric patients was studied. These ratios were compared to the 1:10 (10%) dilution studied in the hemolysis study. The calculated dilution ratios of drug volume:TBV were approximately 1:500 for all pediatric age groups using weight data from CDC growth charts. It should be noted that the average pediatric dose volume ranges from 0.7 mL (1 month old dose) to a maximum volume of 12 mL.

Table 3. 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	mL	500	1:500
9 months	7.4 kg	0.14 mg	.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** 2 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[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

†Dilution of 1: X calculated as follows: X = Average Total Blood Volume / Drug Volume

MO Comment:
When compared to the 1:10 dilution of the hemolysis study, the calculated dilution of approximately 1:500 (for pediatric and adult populations) provides reassurance that the potential for clinically relevant hemolysis is low and does not preclude approval of palonosetron hydrochloride.

There is no regulatory requirement that small volume injectables be isotonic. The proposed palonosetron hydrochloride Dosage and Administration section of the label gives instructions for the infusion line to be flushed with normal saline (an isotonic solution) before and after administration. See below.

Proposed Label (current as of 17 Feb 2016)

2.2 Instructions for Intravenous Administration

- Do not mix with other drugs.
- Flush the infusion line with normal saline before and after administration of Palonosetron Injection.
- Inspect palonosetron solution visually for particulate matter and discoloration before administration.

The volume used to flush an infusion line can vary. However, "typically, in flushing an intravenous cannula, a 5 ml syringe of saline is emptied into the medication port…"[2] The current Aloxi label and the proposed palonosetron hydrochloride labels give instructions for flushing the infusion line before and after drug administration. In these cases, the 2mL dose of palonosetron hydrochloride will effectively be diluted in (b) (4) mL of an isotonic solution (saline).

MO Comment:
The use of normal saline to flush the infusion line prior to and after administration of the 2 mL adult dose of palonosetron hydrochloride will cause the hypotonic drug product to be diluted in a normotonic solution. The exact tonicity of the resultant mixture will be dependent on the volume of normal saline used. However, in all cases, the resultant mixture will have a tonicity >0 mOSM/mL. It is this higher tonicity solution that will reach the patient's blood stream. In summary, the use of a normal saline flush, further lowers the risk of hemolysis related to the use of the hypotonic drug product.

In addition to the hemolysis study included in the current submission, the Applicant also completed a local irritation study in healthy volunteers to address potential safety concerns related to the hypotonicity of palonosetron hydrochloride. The study results

[2] Longmore, Murray; Ian B. Wilkinson; Edward H. Davidson; Alexander Foulkes; Ahmad R. Mafi (2010). *Oxford Handbook of clinical Medicine*.

were submitted during the first review cycle. The primary objective of study EPS-2014-001 was to assess the local irritation by intravenous injection of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection compared with 0.9% Sodium Chloride Injection. The secondary objective of this study was to assess the relative safety and tolerance of the drug product. Dr. Laurie Muldowney reviewed this study and concluded that palonsetron hydrochloride injection was well-tolerated locally. See her review in DARRTS (06/15/2015) for a full review of the study.

Clinical Deficiency #2 (from the CRL)

You have not provided adequate information to establish that your proposed concentration would not increase the potential for dosing errors with palonosetron. To address this deficiency, conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and your proposed concentration (0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error.

Discussion of Applicant's response to Clinical Deficiency Item #2

In their response, the Applicant acknowledged the potential for dosing errors (b) (4)

Indication (b) (4): Chemotherapy-Induced Nausea and Vomiting

- 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

The recommended adult dosage is 0.25 (b) (4) mg administered intravenously as a single dose over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy

(b) (4)

(b) (4)

(b) (4) the Division of Medication Error Prevention and Analysis (DMEPA) has provided recommendations to manage these risks associated with differing concentrations of the reference drug and the proposed drug through label and labeling interventions. DMEPA believes "the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product" (DMEPA labeling Review, Sherly Abraham R. Ph., DARRTS 15 January 2016).

Specifically, DMEPA recommended the following changes to the carton and container labels prior to approval of the current NDA:

1. Add a cautionary statement (b) (4) to the principal display panel that this product is higher in concentration than the reference drug product to avoid dosing errors. For example, (b) (4)
2. To mitigate the risk of confusion with the reference drug's strength and subsequent dosing errors, we recommend revising the statement of (b) (4) (b) (4)
3. Increase the prominence of the established name by increasing the font size.
4. As currently presented, the NDC number is located (b) (4) the carton labeling. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling, in accordance with 21 CFR 207.35(3)(i). Relocate the NDC number from the side panel to the top third of the principal display panel.
5. As currently presented, there are (b) (4) Rx only statements on the side panel. Please move one statement to the bottom right corner of the principal display panel (b) (4).
6. Add a usual dosage statement to the side panel. For example, "Usual dose: See prescribing information".
7. Remove the trailing zero from the strength presentation (0.25 mg/2 mL) to avoid misinterpretation of the product strength.
8. Delete the "(b) (4)" statement since the proposed adult dosage for this formulation is the entire vial (0.25 mg).

9. Revise the "(b) (4)" statement to "2 mL single dose sterile vial" since the term "single dose" accurately describes the correct usage of this product in single patient as a single injection.

MO Comment:
DMEPA's recommendations appear reasonable and the Applicant should make these changes prior to approval of the NDA.

7.4 Supportive Safety Results
N/A

7.4.1 Common Adverse Events

N/A

7.4.2 Laboratory Findings

N/A

7.4.3 Vital Signs

N/A

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant is not proposing a new active ingredient, a new dosage form, a new dosing regimen, or a new route of administration. Therefore, as per Section 505(a)(1) of the Food, Drug and Cosmetic Act, the Sponsor acknowledges that the Pediatric Research Equity Act (PREA) does not apply to this application and therefore the Applicant has requested a full waiver of pediatric studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

The safety update provided with the current submission included data from recently published clinical studies and trials reported in the medical literature from January 2013 to August 2015 for ALOXI. The search to support this safety update included the ubmed database and Google engine. The search terms used included: “palonosetron + adverse events”, “palonosetron + deaths”, “palonosetron + anaphylaxis”, “palonosetron + serotonin syndrome”, palonosetron + case reports”, “palonosetron + safety”, and “palonosetron + QTc”. The Pubmed database was filtered for clinical trials and nonclinical studies separately.

No safety signals were identified that are not already included in palonosetron labeling. During this period, there were no reported deaths attributed to dosed palonosetron in any reported trials.

Table 4. ALOXI Postmarket Safety Summary

PALANOSETRON ONLY	Incidence of Adverse Events in Clinical Trials from 2013 - 2015	Adverse Events Listed on the Aloxi Label for CINV* (2014)	Adverse Events Listed on the Aloxi Label for Aloxi for PONV+ (2014)
Gastrointestinal			
Constipation	3.4%	5%	2%
Diarrhea	0.7%	1%	
Nausea	0.6%		
Hiccups	10.9%	< 1%	
Abdominal distension	2.0%	< 1% (abdominal pain)	
GI disorders	2.3%		
Anorexia	3.3%		< 1%
Nervous System			
Headache	6.2%	9%	3%
Dizziness	11.6%	1%	< 1%
Nervous system disorders	1.1%		
Peripheral sensory neurophathy	1.1%		
Somnolence	19.4%	< 1%	
Drowsiness	34.0%		
Dermatological			
Skin Rash	4.0%	<1%	
Bruise injection	4.0%		
Pruritus	1.0%		1%
Cardiovascular			
Sinus bradycardia	2.0%	< 1%	1%
Muscoloskeletal			
Myalgia	2.5%		
Urinary System			
Urinary retention	6.1%	< 1%	1%
General			
Chills	1.1%		
Asthenia	0.3%	1%	< 1%
Fatigue	0.9%	<1%	

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MO Comment:
The pooled AE data in the postmarket safety summary is difficult to interpret given that the types of studies differed and there was no information provided regarding placebo AEs. There are no serious AEs reported that require further evaluation or specific monitoring. And these data do not suggest that anything other than continued routine postmarket surveillance is necessary at this point.

9 Appendices

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

Labeling negotiations are ongoing. See the final approved label.

9.3 Advisory Committee Meeting

N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AISHA P JOHNSON
02/25/2016

ANIL K RAJPAL
02/25/2016
I concur with Dr. Johnson.

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, M.D., M.P.H. Deputy Director, DGIEP CDER/OND
Subject	Division Director Summary Review
NDA#	207963
Applicant Name	Exela Pharma Sciences
Date of Submission	07 August 2014
PDUFA Goal Date	15 June 2015
(Proposed) Proprietary Name / Established (USAN) Name	Palonosetron Hydrochloride Injection Palonosetron Hydrochloride
Dosage Forms / Strength	Intravenous; 0.25mg/2 mL
Proposed Indication(s)	FOR ADULTS: 1. Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses 2. Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses (b) (4) [redacted]
Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Laurie Muldowney
Pharmacology Toxicology Review	Tracy Behrsing
CMC Review/OBP Review	Raymond Frankewich, Tien Mien Chen, Christina Capacci-Daniel, Vidula Kolhatkar
Microbiology Review	Stephen Langille
Clinical Pharmacology Review	Sandhya Apparaju
DSI	NA
CDTL Review	Refer to MO and Signatory Reviews
OSE/DMEPA	Sherly Abraham, Kendra Worthy
OPDP	Adewale Adeleye
DMPP	Karen Dowdy
DMPH	Miriam Dinatale, Amy Taylor

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
DMPH= Division of Maternal and Pediatric Health
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

1. Introduction

Palonosetron HCl is a 5-HT3 receptor antagonist. This is a 505(b)(2) application. The applicant relies upon FDA's findings of safety and effectiveness found in the currently approved and marketed product Aloxi (palonosetron HCl, Helsinn Care). Aloxi (palonosetron HCl) oral capsule and intravenous injection is approved for the following indications:

- Adults for Chemotherapy Induced Nausea and Vomiting in patients receiving Highly Emetogenic Chemotherapy (acute) (CINV-HEC),
- Adults for Chemotherapy Induced Nausea and Vomiting in patients receiving Moderately Emetogenic Chemotherapy (acute and delayed),
- Adults for Post Operative Nausea and Vomiting (PONV), and
- Pediatric patients older than one month for CINV.

The drug product submitted is a new formulation which differs from the currently approved product in concentration, pH range, and osmolality. Additionally, the product provides an equivalent amount of active ingredient; also, it is a preservative free solution, un-buffered, and hypotonic in comparison. These issues will be considered in my review as they relate to the safety and efficacy of the proposed new formulation of palonosetron HCL intravenous.

2. Background

Presubmission regulatory activity included a preIND meeting with written responses accepted in lieu of the scheduled meeting. The November 30, 2012 meetings reflect our advice regarding a 505(b)(2) application and comments on the tonicity of the proposed product.

(b) (4)

ou will need to adequately justify that (b) (4) *will not affect the safety of the proposed product. This may require the submission of additional safety data."*

On December 19, 2012 further clarification was requested by the sponsor and written advice was provided by DGIEP on February 8, 2013.

> *"The Applicant stated a hemolysis study and injection site sensitivity study in laboratory animals were planned and would be filed with the NDA submission and asked what additional studies should be performed. The Agency reiterated that a local irritation study in healthy volunteers to address potential safety concerns should be completed and that the study protocol, including the proposed number of subjects, should be submitted for FDA review."*
>
> *"The Applicant requested agreement that no BE study is required and a biowaiver would be granted. The Agency reiterated that a biowaiver request, including appropriate justification, must be submitted with the NDA."*

After the submission of this NDA, a Day-74 letter requesting additional information regarding clinical safety and the impact of the change in formulation was requested, specifically:

"1. Provide justification that the design (including sample size and choice of comparator) and results of EPS-2014-001 (b) (4) will not affect the safety of the proposed product. Provide any references for previous publications of local irritation studies that you used to guide the design of your study. This can be included in Section 2.5, Clinical Overview.
2. Provide narratives for all patients who experienced phlebitis and/or irritation, as assessed by the investigator in Study EPS-2014-001.
3. Provide a clinical overview in section 2.5 of the eCTD. The clinical overview should include high level summary information for the listed drug [NDA 021372: Aloxi (palonosetron hydrochloride) injection]. This can be obtained from the RLD approval history as well as the approved full prescribing information. Additional relevant information, including safety information, can also be obtained from published literature, as appropriate. The clinical overview should also include the differences between the proposed formulation and the listed drug formulation and any data that indicate that these differences in formulation will not impact safety or efficacy of the proposed product. Specifically, provide a review of intravenous products with comparable formulation characteristics (no tonicity agent and similar pH) and local infusion site safety profile. A summary of the relevant findings from the local irritation study, EPS-2014-001, should also be included."

The Applicant provided narratives for patients in Study EPS-2014-001, but failed to respond to the remaining clinical requests. Specifically, the Applicant has not yet provided any justification that the change in tonicity from the RLD would not result in any safety issues.

3. Office of New Drug Products:

CMC Review:

Exela's Formulation		**Helsinn Healthcare SA Formulation[1]**	
Ingredients	**Composition**	**Ingredients**	**Composition**
Palonosetron Hydrochloride	0.125 mg/mL (as base)	Palonosetron Hydrochloride	0.25 mg/5 mL (as base) or 0.075 mg/1.5 mL (as base)
Mannitol	Absent	Mannitol	(b) (4)
Disodium edetate	Absent	Disodium edetate	Contains
Citrate buffer	Absent	Citrate buffer	(b) (4)
(b) (4)			

[1] Information regarding Helsinn Healthcare SA, ALOXI® (Palonosetron Hydrochloride) Injection formulation was obtained from the current package insert, vial label, and carton.

(b) (4)

In response to an information request which was included in the 74-day letter (dated October 27, 2014) the applicant provided a comparison of the osmolality of the proposed drug product (with pH adjustment (lots XLNC1306, 7, and 8) and without (lot XLNB1421)) with that of a currently marketed injection of palonosetron (Aloxi® Injection, marketed by Helsinn Healthcare under NDA 21372) referred to below as the RLD. The response was provided in a communication dated March 6, 2015.

Lot Number	pH	Osmolality
XLNC1306	(b) (4)	
XLNC1307		
XLNC1308		
XLNB1421		
RLD – 34002929		
RLD – 34002929		

It is worth noting the difference in the osmolality of the marketed product and the proposed product (XLNC 1305, 1307, 1308, 1421) which is related to the clinical concern for safety (discussed in the clinical section below). The osmolality of human serum is about 278 – 300 mOsm/kg.

The CMC reviewer stated:

> "An expiration date of 24 months is requested for this drug product by the applicant. To justify, stability data through 18 months storage for three lots (in which sodium hydroxide was used to adjust pH) and 12 months storage for one lot (in which no pH adjustment was performed) have been provided in this NDA, and the proposed 24 month expiration date is considered acceptable."

The following is a summary of findings from related reviews which were performed from ONDP review groups:

ESS – Acceptable: April 7, 2015 (Christina Capacci-Daniel)
Biopharm
(Bioavailability) - Not Acceptable: May 2, 2015 (Vidula Kolhatkar)

The applicant did provide acceptable justification regarding the effects of different osmolality on PK with an assessment based on articles regarding the efficacy of the new product which was acceptable to the Biopharm reviewers. However, there was not an

acceptable separate assessment regarding the difference in osmolality on the safety concerns. This will need to be resolved with clinical reviewers prior to granting a biowaiver. At this time there is no need to build a bridge of do PK for this 505(b)(2) submission pending resolution of the above safety issue (Tien Mine Chen email 6/12/2015).

Microbiology- Not Acceptable- sterility issue: May 18, 2015 (Stephen Langille)

The applicant has not provided an adequate description of the holding times associated with the processing of the finished drug product. In order to respond to this deficiency the applicant will have to provide the (b) (4) for the drug product (b) (4).

The Microbiology reviewers also have a comment and recommendation to be sent to the sponsor which is NOT an approvability issue:

(b) (4)

The CMC reviewer stated that labeling has yet to be fully resolved.

The overall recommendation from ONDP is "Not-Ready for Approval"

I concur with the conclusions reached by the chemistry reviewers regarding the deficiencies that need to be resolved prior to approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any new nonclinical studies to support the marketing application. Thus, nonclinical safety assessment of palonosetron is based upon the previously approved drug Aloxi.

The reviewer stated that:

> "The proposed formulation of this drug is hypotonic with a zero osmolality. While the Applicant stated under PIND 116583 that a hemolysis study and injection site sensitivity study in laboratory animals would be submitted in the NDA, these studies

were not included in the marketing application. It is unknown whether there are previously approved products that have zero osmolality".

"There are no nonclinical safety issues for the drug substance (palonosetron), as the Applicant relied on the Agency's previous assessment of the safety of palonosetron. However, in the absence of any nonclinical data supporting the safety of the proposed hypotonic formulation of the drug, there is no basis upon which to make a recommendation from a pharmacology/toxicology standpoint. Based on the hypotonicity of the drug formulation, hemolysis is a potential safety concern."

"For nonclinical safety assessment of the proposed hypotonic formulation of the drug, a hemolysis study is needed".

"Overall, there are no nonclinical safety issues for the drug substance (palonosetron)".

Labeling was addressed by the reviewer and has been incorporated into the current draft label. At this time the labeling could not be finalized.

I concur with the conclusions reached by the non-clinical pharmacology/toxicology reviewer that there is an outstanding safety concern regarding the safety of a hypotonic solution which requires additional non-clinical testing and this precludes approval.

5. Clinical Pharmacology/Biopharmaceutics

In the filing review the Clinical Pharmacology Reviewer stated the following in response to standard filing template:

Did the applicant submit bioequivalence data comparing to-be marketed product(s) and those used in the pivotal clinical trials? NO
Did the applicant provide metabolism and drug-drug interaction information? Yes
Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request? Yes biowaiver (see biopharmacology review)
Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application? No

In the final review, the clinical pharmacology reviewer stated that a review of the to-be marketed product label compared to the RLD (reference listed drug) was made and recommendations to the label were made. Pending final approval of the proposed labeling, the Clinical Pharmacology reviewer stated that this application is acceptable from their point of view.

I concur with the conclusions reached by the clinical pharmacology reviewer that the final decision regarding a biowaiver and agreement with proposed labeling will need to be resolved prior to approval.

6. Clinical Microbiology

See section 3 above. A sterility issue was identified that is listed as a deficiency and precludes approval.

I concur with the conclusions reached by the clinical microbiology reviewer that there is an outstanding sterility issue that preclude approval.

7. Clinical/Statistical-Efficacy

There were not clinical efficacy studies conducted or submitted by the applicant. This application relies on the Agency's findings of efficacy and safety for the currently approved product Aloxi (palonosetron HCl) and other literature.

8. Safety

This 505(b)(2) application relies on the findings of safety and efficacy of Aloxi (palonosetron HCl). As discussed above this formulation differs from the RLD (b) (4) which may affect safety (i.e. injection site reactions or hemolysis).

Overall, for the currently approved Aloxi product, there are three potentially serious side effects of note: hypersensitivity (anaphylaxis), serotonin syndrome (mostly seen with concomitant use of other serotonergic drugs), and the potential for QT prolongation in the class of 5-HT3 receptor antagonists.

The Aloxi sponsor conducted and submitted a thorough QT trial in 2007. 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 study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) in 221 healthy subjects at doses up to 2.25 mg. The package insert includes this information as well as listing QTc prolongation as an infrequently reported adverse reaction (1%) in the clinical trials for Aloxi.

The applicant submitted Study EPS-2014-001: A double blinded, randomized, single dose, parallel local irritation pilot study of intravenous administration of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection of Exela Pharma., USA with 0.9% Sodium Chloride Injection, USP, 2mL of (b) (4) in healthy, adult, human male and/ or female study participants under fasting condition. This is the only safety study conducted by the applicant for this new product. In addition to monitoring local irritation of this intravenous formulation, the applicant also monitored the study patients' clinical status, adverse events and performed clinical laboratory investigations. For complete review of the study results refer to the Medical Officer Review (Laurie Muldowney).

The study is a double-blind, randomized, parallel, local irritation pilot study in which 32 healthy adult subjects were randomized 1:1 to receive the palonosetron or placebo control. The study included a 28-day screening period and a 10-day treatment period. Eligible subjects from the screening period were admitted to the study site the evening prior to dosing and

underwent an overnight fast of at least 10 hours. Subjects were randomized to receive a single dose of either test or control, administered over 30 seconds, and were then monitored as per the schedule described in Table 4 below. Patients were discharged from the study site 48 hours post-dose and returned for subsequent assessments (72, 96, 120, 144, 168, 192, 216 and 240 hours post dose) on an outpatient basis.

The clinical reviewer found the comparator arm acceptable for testing the primary objective.

The reviewer had the following concerns regarding the safety evaluations:

> "Patients were observed thoroughly for injection site reactions, and patients were monitored closely following injections for clinical symptoms associated with hemolysis. The laboratory assessment was insufficient to assess for hemolysis. Peripheral blood smears were not completed and LDH levels were not completed, for example. The frequency of relevant lab work that was completed (e.g., hemoglobin, hematocrit, bilirubin) was insufficient to detect subclinical hemolysis in the study, as labs were drawn prior to infusion and on day 10 only."
>
> "There were no incidents of phlebitis reported more than 4 hours post-dose in subjects receiving either test or control drug. There were no deaths, serious adverse events, or discontinuations due to adverse events during the study. One subject in each treatment arm reported one adverse event (AE), and these AEs were mild in intensity and resolved at the end of the study. There were no clinically significant changes in laboratory parameters, vital signs, or electrocardiograms. "

The reviewer concludes:

> "While no safety signals were observed in the completed clinical study, in the absence of sufficient clinical or nonclinical data supporting the safety of the proposed drug product, there is no basis upon which to recommend approval of this product."

Finally, the reviewer pointed to a concern, regarding the potential use of this product were it to be used in patients with smaller fluid volumes (eg pediatric patients) and the potential for increased risk of hemolysis. The applicant has only requested the adult indication in this application. The clinical reviewer points out that based on the Aloxi dosing for pediatric patients with CINV a maximum dose per body weight could result in the infusion of 12 mL of hypotonic solution. This issue will need to be resolved prior to an approval in the pediatric population.

I agree with the clinical reviewer that issues regarding the safety of this formulation are not resolved, particularly the issues of the safety of the proposed osmolality of this product. Even though this study was small, as the reviewer points out, the evaluation of laboratory tests which could be used as markers for hemolysis were not taken at an appropriate interval for this adverse event to be adequately studied. I agree that the issue of hypotonicity and the potential of significant serious safety issues (e.g. hemolysis) have not been resolved, and that this is a deficiency which will be listed in the Complete Response letter that precludes approval.

9. Advisory Committee Meeting

This is not an NME and no AC was held.

10. Pediatrics and Maternal Health

This application does not include a new active ingredient, a new indication, a new dosage form, a new dosing regimen or a new route of administration. Therefore the application does not trigger PREA. The sponsor request for a waiver is not necessary. This drug was not taken to PERC.

The applicant submitted labeling that only described the adult dosing because of pediatric exclusivity "carve-out". DPMH was consulted for advice regarding labeling of this 505(b)(2) product. Since the approval of Aloxi, on December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). DGIEP requested advice regarding this section of the labeling.

Pregnancy and Lactation labeling was reviewed and recommendations were made to comply with the PLLR. These were incorporated into the draft labeling. Due to the timing of this application DPMH provided wording which could be used in a future approval letter that is important to include at which time this product would be approved.

The Pediatric labeling reviewer stated that upon resubmission of the label it will be important to finalize the particular wording in section 8 due to the pediatric exclusivity and particular "carve out" language will be supplied.

I agree with the DPMH reviewers' conclusions. In addition, because this product is not being approved in the pediatric population, but Aloxi is approved for pediatric patients, it may be important to pay particular attention to the results of the hypotonicity evaluation and safety, given the potential for off label use in pediatric population do to their smaller circulatory volume.

11. Other Relevant Regulatory Issues

DMEPA review comments:

"Aloxi is currently marketed in 0.075 mg/1.5 mL {and 0.25mg/5 mL}. whereas Exela's formulation is 0.25 mg/2 mL (0.125 mg/mL). We reviewed the proposed prescribing information and container label and identified areas in the label and labeling that can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We note that the applicant is proposing a new strength for this product while the active ingredient, dosage form, route of administration (b) (4) is same as the reference listed product. "

In an addendum dated 6/15/2015 by DMEPA, they state that "the potential for dosing errors represents a safety concern that will require further assessment".

The addendum concludes that:

> "We have determined that the introduction of your proposed concentration into the marketplace would increase the potential for dosing errors with palonosetron. We recommend you conduct Human Factors testing to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and your proposed concentration ((0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error".

I agree with the DMEPA recommendations regarding this deficiency and that this will require additional review of the recommended study during the next review cycle.

505(b)(2) Regulatory Issues:

It appears that Helsinn and Roche received notice under 21 CFR 314.52. With respect to any other owner(s) of the patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance

Citizen Petition: (FDA-2015-P-1722; May 13, 2015)

We have conducted a preliminary review and analysis of the issues raised in the citizen petition submitted by Helsinn Healthcare SA (FDA-2015-P-1722) on May 13, 2015, regarding Exela Pharma Sciences, LLC's 505(b)(2) application (NDA 207963) for Palonosetron Hydrochloride Injection. This review has not resulted in any changes to the deficiencies identified in the proposed complete response letter for Palonosetron Hydrochloride Injection. We intend to continue our review of the issues raised in the citizen petition as requested by the Office of Regulatory Policy (ORP) after issuance of the complete response letter."

12. Labeling

The action recommended is a Complete Response, and because of that both OPDP and DMPP have deferred their final review to the next cycle.

The current round of labeling revisions was placed into DARRTS by Jay Carr, that labeling included proposals from Exela which were submitted March 15, 2015. It will be a basis for future labeling negotiations. Mr. Carr documents that Carton and container comments from DMEPA were not submitted to the sponsor this cycle. Finally the Patient Information found at the end of the document does was not reviewed by the Patient labeling team this cycle.

It will be important to describe any safety concerns regarding hypotonicity in the next round of labeling negotiations, especially where patients with smaller blood volumes may be at risk. In addition, clear instructions regarding the concentration and use of this product, based on the results from the human factors study, will need to be reviewed in order to determine if labeling

will be sufficient to promote safe use; including updating proposed the carton and container labeling.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action : Complete Response**

- **Risk Benefit Assessment**

This 505(b)(2) submission relies on the findings of safety and efficacy by the FDA of the reference listed product Aloxi (palonosetron HCl)intravenous as well as other literature and one safety study conducted by the applicant.

The benefit of a new intravenous formulation of palonosetron would be to have a sterile preservative free injectable, which for patients with allergies to preservatives, may be a further benefit compared to the currently approved product. It should be noted that there are other intravenous products in this class which are approved for the proposed indications. The Biopharm reviewer found adequate evidence submitted by the applicant that this formulation should not affect the efficacy of the new product. However, this new formulation has a different pH, and osmolality and concentration than Alxoi. The active ingredient, palonosetron, has been associated with important safety events including anaphylaxis, serotonin syndrome and increased QT prolongation. These adverse events are adequately addressed in the currently approved Aloxi labeling.

Of concern is the failure of the applicant to satisfactorily address the potential serious side effect of hemolysis of the new product related to its hypotonicity. This is the basis for the clinical deficiency issue which will need to be resolved prior to recommending approval. The biowaiver will be reviewed in light of that information. Secondly, the differences in concentration and the potential for medication dosing errors will have to be further studied in a human factors study, given the concentration is approximately 2 times the currently marketed Aloxi product, and the lack of adequate information supplied by the applicant addressing this issue. Finally, the clinical microbiology reviewers reported an issue regarding sterility which must be resolved prior to approval, especially since this product does not contain any preservatives.

Therefore, the risks compared to the benefits of this new hypotonic intravenous palonosetron product are not favorable. Based on this I recommend a Complete Response action.

The following are deficiencies identified in the Complete Response Letter:

CLINICAL

1. You did not provide sufficient information to establish the safety of the proposed formulation of your drug product. You have not established that the hypotonicity of your drug product will not result in clinically relevant hemolysis.

To address this deficiency, data can be provided from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. Particularly address the potential for hemolysis in patients with smaller blood volumes in whom the potential for hemolysis may be greater.

In addition, provide justification that the design (including sample size and choice of comparator) and results of Study EPS-2014-001 support that the tonicity and pH will not pose a significant safety risk.

2. You have not provided adequate information to establish that your proposed concentration would not increase the potential for dosing errors with palonosetron.

To address this deficiency, conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and your proposed concentration ((0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error.

PRODUCT QUALITY

1. You have not provided an adequate description of the holding times associated with the processing of the finished drug product. Provide the (b) (4) for the drug product (b) (4).

2. We cannot grant your request for a Biowaiver until the safety issues related to the hypotonicity of your product, as described above, are resolved.

REGULATORY

1. It appears that Helsinn and Roche received notice under 21 CFR 314.52. With respect to any other owner(s) of the patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

N/A this is a Complete Response and further comment will be made at the time of product approval action.

- **Recommendation for other Postmarketing Requirements and Commitments**

N/A this is a Complete Response and further comment will be made at the time of product approval action.

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/s/

JOYCE A KORVICK
06/15/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207963
Priority or Standard	Standard
Submit Date(s)	07August2014
Received Date(s)	08August2014
PDUFA Goal Date	15June2015
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Laurie Muldowney, MD
Review Completion Date	14May2015
Established Name	Palonosetron Hydrochloride Injection
(Proposed) Trade Name	Palonosetron Hydrochloride Injection
Therapeutic Class	5-HT3 receptor antagonist
Applicant	Exela Pharma Sciences
Formulation(s)	Intravenous
Dosing Regimen	CINV: 0.25 (b) (4) mg IV dose administered over 30 seconds approximately 30 minutes before the start of chemotherapy.

(b) (4)

	(b) (4)
Indication(s)	Chemotherapy-induced Nausea and Vomiting - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
	(b) (4)
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends a Complete Response (CR) action be taken for Palonosetron Hydrochloride Injection for the following 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

(b) (4)

The Applicant, Exela Pharma Sciences, submitted a 505(b)(2) application which relies on the safety and effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372) held by Helsinn Healthcare SA. The active ingredient of Exela's Palonosetron Hydrochloride Injection is the same as that of the Reference Listed Drug (RLD), ALOXI® Injection. Exela's drug product differs from ALOXI® with respect to the active ingredient concentration and excipients used. In comparison to ALOXI® Exela's formulation contains no tonicity agent, buffering agent, or chelating agent. Due to these changes in formulation, the Application could not be submitted as a 505(j) and was therefore filed under 505(b)(2) referencing ALOXI®. The Applicant failed to provide adequate data to support that changes in formulation, specifically the lack of tonicity agent, will not impact the safety of their product. Furthermore, the Applicant failed to respond to an Information Request sent to the Applicant with the Day-74 letter requesting additional information in order to assess that the changes to the formulation would not adversely impact the safety of the product. Therefore, this reviewer recommends that a CR be taken for this application. The specific deficiency is that the Applicant did not provide sufficient information to establish the safety of the proposed formulation of their drug product. Specifically, they have not established that the hypotonicity of their drug product will not result in clinically relevant hemolysis.

In addition, the Applicant's product is a higher concentration than the RLD which has the potential to cause dosing errors. The specific deficiency is that the Applicant has not provided adequate information to establish that the proposed concentration would not increase the potential for dosing errors with palonosetron. Finally, the Applicant failed to provide (b) (4) for the bulk drug product could result in significant microbial growth (b) (4).

For these reasons, this reviewer recommends a Complete Response (CR) action be taken for Palonosetron Hydrochloride Injection.

1.2 Risk Benefit Assessment

Palonosetron Hydrochloride Injection has been marketed in the US since the approval of ALOXI® Injection in 2003. The Application relies on the safety and effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection (NDA 021372). The proposed new formulation provides the equivalent amount of the active ingredient as the RLD but is provided in an unbuffered, hypotonic, preservative free solution.

The availability of Exela Pharma Sciences' product, Palonosetron Hydrochloride would provide an additional preservative free formulation for the prevention of CINV (b) (4) . However, the Applicant has not adequately demonstrated that its product is equivalent to ALOXI® Injection, specifically, the Applicant has failed to provide data supporting that formulation changes will not impact the safety of the product.

The Applicant conducted a single local irritation study in order to address safety concerns stated by the Division in a Written Response Only, pre-IND meeting, dated November 30, 2012, (b) (4) A safety study was performed in 32 healthy adult subjects to assess the local irritation by intravenous injection of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection of Exela Pharma Sciences, LLC, USA with 0.9% Sodium Chloride Injection, USP, 2mL of (b) (4) in healthy adult study participants under fasting conditions. The conclusions of the safety study showed that single 2 mL doses of Exela's Palonosetron Hydrochloride Injection were generally safe and well-tolerated locally following single intravenous administration and local tolerance was comparable to 0.9% Sodium Chloride Injection USP, 2 mL. Given the small sample size, however, the study was designed as a pilot study and not to rule out a specific risk of potential AEs related to the formulation differences. The Applicant selected the 0.9% Sodium Chloride Injection as the comparator as it is isotonic, however, a head-to-head comparison of the Applicant's product with the RLD may have provided more relevant data to support that their formulation changes did not impact the safety of their product, compared with the RLD. Furthermore, the Applicant's study was intended to address the potential for local irritation due to formulation changes and not the potential for hemolysis due to the change in tonicity (the RLD is isotonic and the Applicant's product is hypotonic with a tonicity ~ 0mOsmol/L). For example, the study did not include all relevant laboratory assessments to assess for hemolysis, and those that were included were assessed pre-dose and 10 days following injection only.

An information request was sent to the Applicant with the Day-74 letter requesting additional information in order to assess that the changes to the formulation would not adversely impact the safety of the product, specifically:

1. Provide justification that the design (including sample size and choice of comparator) and results of EPS-2014-001 (b) (4) will not affect the safety of the proposed product. Provide any references for previous publications of local irritation studies that you used to guide the design of your study. This can be included in Section 2.5, Clinical Overview, described above.
2. Provide narratives for all patients who experienced phlebitis and/or irritation, as assessed by the investigator in Study EPS-2014-001.
3. Provide a clinical overview in section 2.5 of the eCTD. The clinical overview should include high level summary information for the listed drug [NDA 021372: ALOXI® (palonosetron hydrochloride) injection]. This can be obtained from the RLD approval history as well as the approved full prescribing information. Additional relevant information, including safety information, can also be obtained from published literature, as appropriate. The clinical overview should also include the differences between the proposed formulation and the listed drug formulation and any data that indicate that these differences in formulation will not impact safety or efficacy of the proposed product. Specifically, provide a review of intravenous products with comparable formulation characteristics (no tonicity agent and similar pH) and local infusion site safety profile. A summary of the relevant findings from the local irritation study, EPS-2014-001, should also be included.

The Applicant provided narratives for patients in Study EPS-2014-001, but failed to respond to the remaining clinical requests. Specifically, the Applicant has not yet provided any justification that the change in tonicity from the RLD would not result in any safety issues.

The RLD has a tonicity of 300 mOSM/kg, whereas the Applicant's product has a tonicity of approximately 0 mOSM/kg. The risks of injecting a hypotonic solution include injection site pain and hemolysis. Injection site pain is a larger concern with intramuscular or subcutaneous injections. As this was not seen in the pilot study completed by the Applicant, this reviewer does not believe this is a major safety concern. Hemolysis would be expected to occur with the injection of a zero osmolar solution, however, the Applicant failed to complete a planned in vitro hemolysis study, so there is no basis upon which to assess the potential for hemolysis from a nonclinical perspective.

The goal for any injectable product is to be isotonic (~280 mOSM/kg); however, this is not an essential requirement for small volume injectables. The Applicant's product is a small volume parenteral, and the indicated dosing regimen would result in only 2mL of solution per dose. Given the low volume of injection when used as indicated, it is unlikely that this would pose a significant safety concern, as the drug product would quickly get diluted in blood. It is not clear to this reviewer; however, what volume of hypotonic solution, injected into the bloodstream, poses a safety risk to patients, and the

Applicant failed to provide any data to support this. Inappropriate infusions of large volumes of free water for injection (i.e., 500mL) leading to patient deaths have been documented. While it is unlikely that the 2mL indicated dose in adult patients would lead to significant safety concerns, the pediatric dose for ALOXI, for ages 1 month to 17 years, is .02 mg/kg with a maximum dose of 1.5mg. The maximum dose would result in 12mL of hypotonic solution injected into a pediatric patient weighing 75kg. Furthermore, while the volume of injection would be less for smaller pediatric patients, these patients would also have a lower blood volume, increasing the potential risk from a hypotonic solution. For example, infant blood volume is estimated at approximately 400mL compared to 5L for an adult male.

In summary, the Applicant relies on the safety and effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372), however, the Applicant failed to provide sufficient data to justify that changes (b) (4) would not impact the safety of their product. While the volume of injection, when administered according to the labeling, minimizes the potential for serious adverse effects related to hemolysis, it is anticipated that this product will be used in pediatric patients given the RLD is approved in this age group.

While the availability of a preservative-free product, presented as a single dose vial, may provide benefit and added options to patients, the lack of tonicity does not appear to be beneficial to patients and may pose a risk, particularly when used in pediatric patients. There is currently a carve out for pediatrics due to RLD exclusivity which expires 27Nov2017, however, ALOXI® is approved to 1 month, and pediatric use is likely for this product without clear steps to ensure it is not used in this population. Without data to support the safety of the administration of this hypoosmolar product, such as literature support or a listing of other marketed agents whose osmolality exposure is equivalent or similar to their product without safety concerns, this reviewer believes the potential risks of the product outweigh the potential benefits.

In addition, the Applicant's product is a higher concentration than the RLD. Based on preliminary review of the issues raised and discussion with DMEPA, we have determined that the introduction of a higher concentration has the potential to cause dosing errors. DMEPA noted that post-marketing evaluations of errors with other drug products has identified a risk for error with introduction of new concentrations. The specific deficiency is that the Applicant has not provided adequate information to establish that the proposed concentration would not increase the potential for dosing errors with palonosetron. To address this deficiency, the Applicant should conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and the proposed concentration ((0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error.

Finally, the Product Quality Microbiology review identified one deficiency, specifically the Applicant failed to provide [redacted] (b) (4) for the bulk drug product. This deficiency could result in significant microbial growth [redacted] (b) (4). To address this deficiency, the Applicant should provide [redacted] (b) (4) for the bulk drug product.

As previously stated, based on the deficiencies described above, this reviewer believes the potential risks of the product outweigh the potential benefits. A Complete Response is recommended outlining the deficiencies and strategies to address the deficiencies.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A

1.4 Recommendations for Postmarket Requirements and Commitments

N/A

2 Introduction and Regulatory Background

2.1 Product Information

Palonosetron hydrochloride ((3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[*de*]isoquinoline hydrochloride) a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple approved products for the proposed indication [redacted] (b) (4) See **Table 1** below.

Table 1: Approved Products for the Proposed Indications

DRUG NAME Formulations (Sponsor)	Initial Approval Date	Indications
5-HT3 Receptor Antagonists		
ZOFRAN® (ondansetron) Oral tablets Orally disintegrating tablets Oral solution Intravenous injection (GlaxoSmithKline)	1991	**Adults and Pediatrics** **CINV, CINV-HEC, CINV-MEC, and PONV**
ANZEMET (dolasetron mesylate) Oral tablet Oral solution Intravenous injection (Sanofi-Aventis U.S. LLC)	1997	**Adults and Pediatrics** **CINV and PONV**
KYTRIL (granisetron) Oral tablet Oral solution Intravenous injection (Roche Pharmaceuticals)	1993	**Adults** **CINV and PONV** **Pediatrics** **CINV (> 2 years)**
ALOXI (palonosetron HCl) Oral capsule Intravenous injection (Helsinn Healthcare)	2003	**Adults** **CINV-HEC (acute), CINV-MEC (acute & delayed), PONV** **Pediatrics** **CINV (≥ 1 month)**
SANCUSO (transdermal granisetron) (ProStrakan)	2008	**Adults** **CINV-HEC, CINV-MEC** ***No Approved Pediatric Indications***
H1 Receptor Antagonists		

DRUG NAME Formulations (Sponsor)	Initial Approval Date	Indications
Hydroxyzine hydrochloride oral capsule oral suspension intramuscular injection (Generic) *Note: oral syrups and tablets are available but approved for indications other than antiemesis.*	1957	**Adults** **NV** **Pre- and Postoperative adjunctive medication** **Pediatrics** **NV** **Pre- and Postoperative adjunctive medication**
NK1 Receptor Antagonists		
EMEND (aprepitant/fosaprepitant dimeglimine) Oral capsule Intravenous injection (Merck)	2003	**Adults** **CINV-HEC and CINV-MEC (in combination with other antiemetics)** **PONV** ***No Approved Pediatric Indications***
Fixed Dose Combination Products		
AKYNZEO (netupitant ; palonosetron hydrochloride) Oral capsule (Helsinn Healthcare)	2014	**Adults** **CINV-HEC and CINV-MEC** ***No Approved Pediatric Indications***

2.3 Availability of Proposed Active Ingredient in the United States

Palonosetron hydrochloride was first approved on July 25, 2003 under NDA 021,372 as ALOXI® Injection and is currently marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues included in the labeling for ALOXI® include:

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT3 receptor antagonists.
- 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.

In addition, there exists the serious risk of cardiac arrhythmias, such as QTc prolongation with 5-HT3 receptor antagonists. Cardiac events have been primarily documented with intravenous administration of these drugs. The FDA has contraindicated the use of dolasetron I.V. in adults and children for the prevention of CINV due to serious cardiac arrhythmias, and the FDA issued a drug safety communication for ondansetron I.V. related to QT prolongation observed at the 32 mg single I.V. administered dose.

The ALOXI® sponsor conducted and submitted a thorough QT trial in 2007. 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 study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) in 221 healthy subjects at doses up to 2.25 mg. The package insert includes this information as well as listing QTc prolongation as an infrequently reported adverse reaction (1%) in the clinical trials for ALOXI®.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 116,583 was submitted on November 15, 2013. Presubmission regulatory activities related to this submission included one scheduled face-to-face preIND meeting between the Applicant and FDA which was subsequently cancelled and follow-up meeting advice.

A type B, pre-IND meeting was scheduled for November 30, 2012. Upon receipt of the FDA's preliminary responses for the Type B, pre-IND meeting, the Sponsor accepted FDA's preliminary responses and cancelled the face-to-face meeting. The purpose of the meeting was to discuss the development plans for palonosetron hydrochloride injection, 0.125 mg/mL. Specific advice provided by the FDA included:

- The FDA agreed that a 505(b)(2) application would be an acceptable approach based on the information provided and had the following specific advice:
    - If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose

to rely to demonstrate that such reliance is scientifically justified. Alternatively, you may request a biowaiver under 21 CFR 320.22.

- If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.
- We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

- (b) (4) ou will need to adequately justify that these changes will not affect the safety of the proposed product. This may require the submission of additional safety data.

The Applicant requested clarification on FDA's meeting preliminary in correspondence dated December 19, 2012 and written advice was provided on February 8, 2013. Specific questions by the Sponsor and advice provided by the Agency included:

- The Applicant stated a hemolysis study and injection site sensitivity study in laboratory animals were planned and would be filed with the NDA submission and asked what additional studies should be performed. The Agency reiterated that a local irritation study in healthy volunteers to address potential safety concerns should be completed and that the study protocol, including the proposed number of subjects, should be submitted for FDA review.

- The Applicant requested agreement that no BE study is required and a biowaiver would be granted. The Agency reiterated that a biowaiver request, including appropriate justification, must be submitted with the NDA.

2.6 Other Relevant Background Information

There is no other relevant background information, except as discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was poor. The Application was electronic, non-ectd format, and the Table of Contents contained appropriately placed links to allow navigation throughout the Application. The local irritation study Clinical Study Report was incorrectly located in Section 4 (Nonclinical) instead of Section 5 (Clinical). No Clinical Overview or Clinical Summary was provided, and the only discipline summary included was the Quality Summary

3.2 Compliance with Good Clinical Practices

A statement of Good Clinical Practice was included on the cover page of the local irritation study Clinical Study Report.

3.3 Financial Disclosures

No clinical trials were conducted which the Applicant relied on to establish efficacy.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A comparison of the ingredients in Exela's Palonosetron Hydrochloride Injection, 0.125 mg/mL with Helsinn Healthcare SA's ALOXI® (palonosetron hydrochloride) Injection is shown in **Table 2** below.

Table 2: Side-by-Side Comparison of Exela's Palonosetron Hydrochloride and the Reference Listed Drug

	Exela's Palonosetron Hydrochloride (palonosetron hydrochloride) Injection	ALOXI® (palonosetron hydrochloride) Injection (RLD)
Active Ingredient	Palonosetron Hydrochloride	Palonosetron Hydrochloride
Strength(s)	0.125 mg/mL (as base)	0.25 mg/5 mL (as base) or 0.075 mg/1.5 mL (as base)
Configuration/label	0.25 (b) (4) mg/2 mL (as base)	0.25 mg/5 mL (as base) or 0.075 mg/1.5 mL (as base)
Excipients	(b) (4)	Mannitol Disodium edetate Citrate buffer
Solvent		Water for Injection , USP
Dosage Form		Injection, solution
Route of administration	Intravenous	Intravenous
(b) (4)		

The active ingredient concentration of the Exela product is 0.125 mg/mL (as base), compared to ALOXI® which contains 0.25mg/5 mL (as base) or 0.075 mg/1.5 mL (as base). Exela's formulation contains no Mannito (b) (4) disodium edetate (b) (4) or citrate (b) (4). Exela's original formula may have contained sodium hydroxide and hydrochloric acid as pH adjusters, if needed. These are commonly used excipients as pH control agents and are generally recognized as safe (GRAS). The Applicant subsequently submitted an amendment to the NDA removing the use of these pH adjusters, however.

Reviewer Comments: The Applicant removed th (b) (4)

results in a hypotonic solution, which may pose a safety risk (i.e., hemolysis) for patients with low blood volume and/or if a larger volume of drug product is administered. While this product will only be indicated in adults, it is likely that it will be used off label in pediatrics. Pediatric dosing is weight based and in some situations will result in a larger dose administered. Furthermore, ALOXI® is indicated down to 1 month of age. Infants have blood volumes substantially less than adults, which could potentially lead to hemolysis. Data is needed to support the use of a hypotonic injection in this context.

The Applicant's product is a higher concentration than the RLD. The Sponsor of the RLD (Helsinn Healthcare) submitted a citizen petition on 13May2015 that this would result in medication errors. Based on preliminary review of the issues raised and discussion with DMEPA, we have determined that the introduction of a higher

concentration has the potential to cause dosing errors. DMEPA noted that post-marketing evaluations of errors with other drug products has identified a risk for error with introduction of new concentrations. For example, FDA has received post-marketing reports of medication errors between 2 morphine oral solution drug products (20mg/mL and 20mg/5mL), some of which resulted in death. DMEPA recommends further assessment, including Human Factors testing, to characterize the risk of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and the proposed concentration (0.125mg/mL) and to demonstrate that the Applicant's proposed strategies to address the identified risks mitigates the potential for error.

4.2 Clinical Microbiology

There are no clinical microbiology issues, as this product is not an antimicrobial/antibiotic.

The Product Quality Microbiology review identified one deficiency, specifically the Applicant failed to provide (b) (4) for the bulk drug product. This deficiency could result in significant microbial growth (b) (4) A complete response to microbiology deficiencies is required prior to a recommendation on approvability. For more information see the Product Quality Microbiology Review by Stephen Langille, PhD.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical/toxicology studies were submitted in support of NDA 207963. The Applicant relies on the nonclinical/toxicology studies conducted by Helsinn Healthcare SA in support of ALOXI® (NDA 021372). There are no major efficacy or safety issues for the drug substance.

The Applicant stated under PIND 116583 that a hemolysis study and injection site sensitivity study in laboratory animals would be submitted in the NDA, and these studies were not included. Based on the hypotonicity of the product, the nonclinical reviewer states that hemolysis is a potential safety concern. In the absence of any nonclinical data supporting the safety of the proposed hypotonic formulation, the nonclinical reviewer states there is no basis upon which to make a recommendation from a pharmacology/toxicology standpoint. For more information see the Nonclinical Review by Tracy Behrsing, PhD.

4.4 Clinical Pharmacology

No new clinical pharmacology information was submitted in support of this application. There are no major efficacy or safety issues from Clinical Pharmacology, which

recommends approval. For more information see the Clinical Pharmacology Review by Sandhya Apparaju, PhD.

The Applicant requested a waiver of the in vivo bioequivalence study requirement as allowed under 21CFR 320.22(b)(1)(i) and (ii). The Applicant proposes that the drug product's self-evident in vivo bioavailability or bioequivalence is based on the fact that it is a parenteral drug product and has the same active ingredient, dosage form, route of administration, and indications as the RLD, ALOXI® (palonosetron hydrochloride) Injection. Based on concerns regarding the osmolality of the proposed drug product, Biopharmaceutics determined that a biowaiver cannot be granted. For more information see the Biopharmaceutics Review by Tapash Ghosh, PhD.

4.4.1 Mechanism of Action

As per the ALOXI® package insert.

4.4.2 Pharmacodynamics

As per the ALOXI® package insert.

4.4.3 Pharmacokinetics

As per the ALOXI® package insert.

5 Sources of Clinical Data

No clinical trials were conducted to demonstrate the efficacy of the product; however, a local irritation study was completed in response to FDA request during the pre-IND meeting. Specifically, FDA stated that (b) (4) the Sponsor would need to adequately justify that these changes will not affect the safety of the proposed product. This justification may require the submission of additional safety data.

5.1 Tables of Studies/Clinical Trials

Table 3: Table of Studies

Study ID	Study Design	Study Population	Study Enrollment and Treatment Arms	Primary Objective
EPS-2014-001	Single center, double-	Healthy adult males and females between	32 subjects (22 male, 10 female) - 16 palonosetron	- to assess the local irritation by IV injection of Palonosetron

	blind, randomized, single dose, parallel local irritation pilot study	the ages of 18 and 45 years	0.25mg/2 mL IV - 16 sodium chloride injection, USP, 0.9% 2 mL IV	Hydrochloride 0.25mg/2mL Injection or 0.9% Sodium Chloride Injection, USP 2mL - there were no efficacy or pharmacokinetic assessments

Source: Reviewer's Table Summarized from Applicant's Local Irritation Study Clinical Study Report

5.2 Review Strategy

For this NDA submission, no adequate and well-controlled trials were conducted to demonstrate the effectiveness of the investigational product. The Applicant is relying on the safety and effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372). Because the Applicant's product differs from ALOXI® with respect to the excipients used, specifically, Exela's formulation contains no tonicity agent, buffering agent, or chelating agent, the Applicant conducted a pilot local irritation study to assess if these changes affected the safety of the product. The local irritation study was reviewed in detail. Details of the protocol are included in Section 5.3 below, and safety results are described in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title:
EPS-2014-001. A double blinded, randomized, single dose, parallel local irritation pilot study by intravenous administration of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection of Exela Pharma., USA with 0.9% Sodium Chloride Injection, USP, 2mL of (b) (4) in healthy, adult, human male and/ or female study participants under fasting condition

Study Overview:
Study EPS-2014-001 was a single-center, double-blind, randomized, two-treatment, parallel local irritation pilot study completed under fasting conditions. Thirty-two healthy adult participants received a single dose of Palonosetron Hydrochloride injection or Sodium Chloride Injection over 30 seconds and their IV sites were assessed for phlebitis and local infiltration at prespecified intervals over the next 10 days. Adverse events were monitored by nursing and medical observations, as well as spontaneous reporting throughout the study.

Primary Objectives:

To assess the local irritation by intravenous injection of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection of Exela Pharma., USA with 0.9% Sodium Chloride Injection, USP, 2mL of (b) (4) in healthy, adult, and human study participants under fasting conditions.

Secondary Objectives:
To monitor clinical status, adverse events and laboratory investigations and assess relative safety and tolerance of Palonosetron formulations under fasting conditions.

Study Design:
The study is a double-blind, randomized, parallel, local irritation pilot study in which 32 healthy adult subjects were randomized 1:1 to receive the palonosetron or placebo control. The study included a 28-day screening period and a 10-day treatment period. Eligible subjects from the screening period were admitted to the study site the evening prior to dosing and underwent an overnight fast of at least 10 hours. Subjects were randomized to receive a single dose of either test or control, administered over 30 seconds, and were then monitored as per the schedule described in **Table 4** below. Patients were discharged from the study site 48 hours post-dose and returned for subsequent assessments (72, 96, 120, 144, 168, 192, 216 and 240 hours post dose) on an outpatient basis.

5.3.2 Key Inclusion Criteria

1. Non-smoking healthy male or female between 18 and 45 years of age, inclusive.
2. Females must meet at least one of the following criteria:
    a. sexually inactive (abstinent) for at least 14 days prior to the first dose and throughout the study
    b. postmenopausal
    c. using acceptable birth control methods (specified in protocol) :
3. Weight between 50 kg (110 lb.) and 90 kg (198 lb.), inclusive, and BMI 18-35 kg/m2, inclusive.
4. No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during screening.
5. Ability to complete the study in compliance with the protocol.
6. Ability to understand and provide written informed consent.

5.3.3 Key Exclusion Criteria

1. A clinically significant laboratory abnormality or other clinical findings indicative of a clinically significant exclusionary disease (including but not limited to renal, hepatic, gastrointestinal, cardiovascular, neurological disease).
2. A history of hypersensitivity to study drug or any other component of the formulation.

3. A positive hepatitis screen
4. A positive test result for HIV antibody
5. Positive results from a screen for alcohol or substances of abuse at screening or upon admission to the clinical research unit.
6. A positive pregnancy test at screening or upon admission to the clinical research unit, or subject is lactating, if the subject is female.
7. A recent history of alcoholism (< 2 years) or of moderate alcohol use (greater than an average of 3 alcoholic drinks per day or a total of 21 alcoholic drinks per week).
8. Use of any recreational drugs within the past year or a previous history of drug abuse.
9. A clinically significant ECG abnormality.
10. A history of difficulty with phlebotomy.
11. Use of any prescription drug therapy within 14 days prior to receiving study drug.
12. Use of any over-the-counter drugs for therapeutic purposes within 48 hours prior to receiving study drug
13. Use of dietary or herbal supplements within 48 hours prior to receiving study drug. Consumption of any caffeine- or xanthine-containing foods or beverages within 24 hours prior to receiving study drug.
14. Consumption of alcohol within 24 hours prior to receiving study drug
15. Consumption of any grapefruit or grapefruit-containing juices within 72 hours prior to receiving study drug.
16. Current smoker or user of any tobacco products.
17. Any condition or illness which in the opinion of Investigator would interfere with the participant's ability to provide informed consent, comply with study instructions, possibly confound interpretation of study results, or endanger the participant if he or she took part in the trial.
18. Use of an investigational drug or product or participation in a drug research study within 30 days prior to receiving study drug.

5.3.4 Study Medication, Concomitant Medications

Study participants were randomized to one of 2 treatments according to a randomization schedule which was generated prior to study initiation.

- Test Product: Palonosetron HCl, 0.25 mg/2 mL, Injection, manufactured by Exela Pharma Sciences, LLC, USA
- Control: Sodium Chloride Injection, USP, 0.9%, 2 mL, manufactured by (b) (4)

Study participants were required to undergo an overnight fast ≥ 10 hours prior to drug administration. Participants were placed in a supine position, and 2 mL of study drug was administered to participants over a period of 30 seconds. The infusion line was flushed with 0.5mL of normal saline before and after drug administration.

Reviewer Comments: This reviewer believes ALOXI® would have been a more appropriate control, in order to assess if their product has a different safety profile (i.e., local irritation) than the RLD. However, the selected control, Sodium Chloride Injection, USP, 0.9% has an osmolarity of 300 mOsmol/L and is thus isotonic. The primary formulation difference which could lead to safety concerns, in this reviewer's opinion, is the lack of a tonicity agent in the investigational product. With this in mind, comparing the test product (osmolarity ~ 0 mOsmol/L) with Sodium Chloride injection (osmolarity ~300 mOsmol/L) is appropriate.

5.3.5 Study Visits and Procedures

Subjects were discharged from the study site approximately 48 hours post-dose, and returned on an out-patient basis for scoring at 72, 96, 120, 144, 168, 192, 216 and 240 hours post-dose. Blood and urine were collected for clinical laboratory tests, and a symptom directed physical examination was performed prior to discharge from the study.

Table 4: Schedule of Procedures

Study Phase	Screening	Study Days				Study Exit
Activity	Within 28 days prior to dosing (D – 28 to D – 1)	Check-In (D -1)	Dosing Day (D1)	Checkout (D2)	Outpatient Visits[a]	Final Exit (D10)
Informed Consent	X					
Medical History, Demographics	X	X				
Physical Examination	X					
Inclusion/Exclusion Criteria	X					
Clinical assessment[b], record of concomitant meds	X	X	X	X	X	X
ECG	X		X			X
Vital Signs	X	X	X	X	X	X
Labs[c] (Hematology, Chemistry, Urinalysis)	X					X
HIV/Hepatitis B&C Screen, RPR	X					
Urine Drug Screening		X				
Urine pregnancy	X	X				X
Drug dosing			X			
Scoring[d] (phlebitis and infiltration)			X	X	X	
Adverse Event Monitoring		X	X	X	X	X

Source: Applicant Protocol EPS-2014-001.
[a] Outpatient visits will occur at 72, 96, 120, 144, 168, 192, 216 and 240 hours post dose for scoring
[b] Symptom directed physical examination
[c] Labs will include hematology (hemoglobin, hematocrit, RBC, WBC with diff, platelet count), chemistry (carbon dioxide, Ca, Cl, cholesterol, creatinine, glucose, Alk Phos, K, Na, AST, ALT, BUN, total bili), and urinalysis (color, appearance, pH, specific gravity, bilirubin, blood, glucose, ketones, protein, microscopic exam)
[c] The IV site will be assessed using the Phlebitis and Infiltration scale scoring at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post dose.

Reviewer Comments: The primary difference between the Applicant's formulation and the RLD is the difference in pH and the osmolality. The Applicant's formulation is hypotonic, and the primary risks associated with the lack of tonicity agent in the investigational product are hemolysis and local tissue irritation. Patients were observed thoroughly for injection site reactions, and patients were monitored closely following injections for clinical symptoms associated with hemolysis. The laboratory assessment was insufficient to assess for hemolysis. Peripheral blood smears were not completed and LDH levels were not completed, for example. The frequency of relevant lab work that was completed (e.g., hemoglobin, hematocrit, bilirubin) was insufficient to detect subclinical hemolysis in the study, as labs were drawn prior to infusion and on day 10 only.

5.3.6 Control Procedures

This was a double-blind pilot study in which subjects were randomized to one of 2 treatments according to a randomization schedule.

5.3.7 Outcome Measurements

The primary outcome measures will assess the incidence of phlebitis and local infiltration at the IV site. The IV site will be assessed using the Phlebitis and Infiltration scale scoring at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post dose. The primary outcome will compare the incidence rate of phlebitis cases expressed as a percentage of the exposed population. Odds ratios for the two groups will be calculated with 95% CI. Skin reactions were evaluated by 2 independent observers and scored according to the following scales:

Table 5: Phlebitis Scale

Skin Appearance	Score
No Symptoms	0
Erythema at access site with or without pain	1+
Pain at access site with erythema and/or edema	2+
Pain at access site with erythema and/or edema, streak formation, palpable venous cord	3+

Source: Applicant Protocol EPS-2014-001.

Table 6: Infiltration Scale

Skin Appearance	Score
No symptoms	0
Skin blanched, edema < 1 inch in any direction, cool to touch, with or without pain	1
Skin blanched, edema 1 to 6 inches in any direction, cool to touch, with or without pain	2
Skin blanched, translucent; gross edema > 6 inches in any direction; cool to touch; mild to moderate pain; possible numbness	3
Skin blanched, translucent; skin tight, leaking; skin discolored, bruised, swollen; gross edema > 6 inches in any direction; deep pitting tissue edema; circulatory impairment; moderate to severe pain; infiltration of any amount of blood product, irritant or vesicant	4

Source: Applicant Protocol EPS-2014-001.

The safety and tolerability of palonosetron will also be assessed by the incidence of treatment emergent adverse

5.3.8 Statistical Information

Formal sample size calculations were not conducted for this study.

Subjects who receive at least one dose of the study drug will be included in the safety evaluations.

Phlebitis Scores:

- The site of venous access was examined at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours post-dose.
- The maximum of the two independent observers' phlebitis scores for each time point was used for all analyses.
- Phlebitis scores were summarized at each time point along with the highest score each participant received, and the number of non-zero severity scores were summarized at each time point and overall.
- The incidence rate is the occurrence of phlebitis cases in a time period of total exposure time points (240 hours). The incidence of phlebitis per 100 people, defined as phlebitis score ≥ 1+, was determined at each time point and overall. The odds ratio and associated 95% confidence interval were also calculated.

Infiltration Scores:

- The site of venous access was examined at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours post-dose.
- The maximum of the two independent observers' phlebitis scores for each time point was used for all analyses.
- Infiltration scores will be recorded at time points of occurrence.

Descriptive statistics will be calculated for continuous data and count and percentage for categorical data.

5.3.9 Protocol Amendments

There were no protocol amendments for this study.

6 Review of Efficacy

Efficacy Summary

No clinical trials were submitted in this 505(b)(2) application to support the efficacy of palonosetron hydrochloride injection. The Applicant relies on the effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372) held by Helsinn Healthcare SA.

6.1 Indication

Palonosetron Hydrochloride Injection is a serotonin subtype 3 (5-HT3) receptor antagonist indicated 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

(b) (4)

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

Based on the safety data reviewed from Study EPS-2014-001, a double blinded, randomized, single dose, parallel local irritation pilot study, this medical reviewer finds that Palonosetron Hydrochloride Injection was well-tolerated locally, however, the study was not sufficient to draw conclusions on the overall safety of the drug product.

A total of 32 patients were included in the pilot local irritation study, with 16 patients receiving single dose Palonosetron Hydrochloride Injection 0.25 mg/2mL and 16 patients receiving single dose 0.9% Sodium Chloride Injection, USP 2 mL. Patients were observed in hospital for 48 hours and evaluated for local signs of phlebitis or infiltration at the IV site. Continued observations occurred during out-patient visits through Day 10. The incidence rate of phlebitis and infiltration was comparable between Palonosetron Hydrochloride Injection and 0.9% Sodium Chloride. There were no incidents of phlebitis reported more than 4 hours post-dose in subjects receiving either test or control drug. There were no deaths, serious adverse events, or discontinuations due to adverse events during the study. One subject in each treatment arm reported one AE, these AEs were mild in intensity and resolved at the end of the study. There were no clinically significant changes in laboratory parameters, vital signs, or electrocardiograms.

The study was designed as a pilot study and not to rule out a specific risk of potential AEs related to the formulation differences. Given the small number of healthy subjects studied and the use of sodium chloride as a comparator, this reviewer cannot draw conclusions on the comparability of Palonosetron Hydrochloride Injection with ALOXI® Injection, as it relates to local irritation. Furthermore, based on the hypotonicity of the drug product, hemolysis is a potential safety concern and, in this reviewer's opinion, was inadequately assessed in the pilot study. While patients were monitored for AEs, the laboratory assessment was insufficient. Not all needed labs were included in the protocol (e.g., peripheral blood smears and LDH levels were not assessed), and the frequency of relevant lab work that was completed (e.g., hemoglobin, hematocrit, bilirubin) was insufficient to detect subclinical hemolysis in the study, as labs were drawn prior to infusion and on day 10 only. While no safety signals were observed in the completed clinical study, in the absence of sufficient clinical or nonclinical data supporting the safety of the proposed drug product, there is no basis upon which to recommend approval of this product.

An information request was sent to the Applicant with the Day-74 letter requesting the following information:

1. Provide justification that the design (including sample size and choice of comparator) and results of EPS-2014-001 (b) (4) will not affect the safety of the proposed product. Provide any references for previous publications of local irritation studies that you used to guide the design of your study. This can be included in Section 2.5, Clinical Overview, described above.
2. Provide narratives for all patients who experienced phlebitis and/or irritation, as assessed by the investigator in Study EPS-2014-001.
3. Provide a clinical overview in section 2.5 of the eCTD. The clinical overview should include high level summary information for the listed drug [NDA 021372: ALOXI® (palonosetron hydrochloride) injection]. This can be obtained from the RLD approval history as well as the approved full prescribing information. Additional relevant information, including safety information, can also be obtained from published literature, as appropriate. The clinical overview should also include the differences between the proposed formulation and the listed drug formulation and any data that indicate that these differences in formulation will not impact safety or efficacy of the proposed product. Specifically, provide a review of intravenous products with comparable formulation characteristics (no tonicity agent and similar pH) and local infusion site safety profile. A summary of the relevant findings from the local irritation study, EPS-2014-001, should also be included.

The Applicant provided a response to item number 2 (narratives) but has not provided the other information requested. Data is needed to support that the formulation changes, specifically the change in tonicity, of this product will not result in any safety issues. Data justifying this can be obtained from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. As none of this data was provided in support of this application, this reviewer recommends a Complete Response (CR) action be taken.

A brief summary of the completed pilot study is below.

7.1 Methods

The safety analysis set was defined as all subjects enrolled in the pilot local irritation study who received at least one dose of study drug. Sixteen (16) healthy subjects received Palonosetron Hydrochloride Injection and 16 0.9% Sodium Chloride Injection, USP. All subjects received a single dose of the study drug and were included in the safety assessment.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This application included only 1 clinical study, EPS-2014-001. This study was intended to evaluate the safety of palonosetron and specifically, to assess the impact of the formulation on local phlebitis and infiltration.

Table 7: Study EPS-2014-001

Study ID	Study Design	Study Population	Study Enrollment and Treatment Arms	Primary Objective
EPS-2014-001	Single center, double-blind, randomized, single dose, parallel local irritation pilot study	Healthy adult males and females between the ages of 18 and 45 years	32 subjects (22 male, 10 female) - 16 palonosetron 0.25mg/mL IV - 16 sodium chloride injection, USP, 0.9% 2 mL IV	- to assess the local irritation by IV injection of Palonosetron Hydrochloride 0.25mg/2mL Injection or 0.9% Sodium Chloride Injection, USP 2mL - there were no efficacy or pharmacokinetic assessments

Source: Reviewer's Table Summarized from Applicant's Local Irritation Study Clinical Study Report

7.1.2 Categorization of Adverse Events

An adverse event was defined as any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Adverse events were further graded by the Principal Investigator based on severity and relationship to study drug as shown in **Table 8** and **Table 9**.

Table 8: Adverse Event Severity Grading

Degree	Description
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Source: Applicant Protocol EPS-2014-001.

Table 9: Adverse Event Relationship to Study Drug

Degree	Description
Probably	There is evidence of exposure to the study drug; the temporal sequence of the AE onset relative to medication administration is reasonable; the AE is more likely explained by the treatment than by another cause.
Possibly	There is evidence of exposure to the study drug; the temporal sequence of the AE relative to the medication administration is reasonable; the AE could have been due to another equally likely cause.
Not related	There is no evidence of exposure to the study drug; there is another more likely cause of the AE.

Source: Applicant Protocol EPS-2014-001.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

Safety assessments included monitoring adverse events, laboratory assessments (hematology, chemistry, and urinalysis), vital sign analysis, ECGs, physical examination findings, and assessment of phlebitis and infiltration using the scales described in Table 5 and Table 6.
Vital signs were performed after subjects were seated for a minimum of 5 minutes. Systolic and diastolic blood pressure, pulse rate, respiratory rate were assessed at screening, pre-dose, and at 2, 6, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. A full physical examination was performed at screening and a symptoms-directed physical examination was performed prior to discharge from the study. A resting ECG was performed at screening and again 4 and 24 hours post-dose.

Safety related laboratory testing was completed at screening and at discharge Day 10. Laboratory parameters collected included:

- Chemistry: BUN, creatinine, total bilirubin, glucose, alkaline phosphatase, CO2, sodium, potassium, chloride, calcium, total cholesterol
- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, platelet count and white blood cell (WBC) count with differential.
- Urinalysis: Color, Appearance pH, specific gravity, protein, glucose, blood, ketones, bilirubin, and microscopy.

Reviewer Comments: The local irritation study completed was not powered to rule out a difference in phlebitis or infiltration, nor was it designed to assess the overall safety of Palonosetron Hydrochloride Injection. The Applicant is relying on the safety of ALOXI®, however, this reviewer does not believe the difference in tonicity between formulations

was adequately addressed. Specifically, the safety assessments were not adequate to assess for hemolysis as a result of infusion of a hypotonic formulation. Relevant labs such as lactate dehydrogenase and unconjugated bilirubin were not completed. Lab work that was completed (e.g., hemoglobin, hematocrit, bilirubin) was completed pre-dose and not again until Day 10. Vital signs were also not assessed until 2 hours following infusion.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The single dose of Palonosetron Hydrochloride 0.25 mg/ 2 mL Intravenous Injection is the adult dosage recommended in the management of chemotherapy induced nausea and vomiting and is greater than the adult dosage for postoperative nausea and vomiting (0.075mg). The dose was administered over 30 seconds, which is consistent with the labeled dosage and administration.

The study enrolled healthy adult patients. Table 10 below shows the demographics and baseline characteristics of the safety population.

Table 10: Demographics and Baseline Characteristics – Safety Population

Demographic	Statistics	Palonosetron Hydrochloride 0.25mg/2mL injection N = 16	0.9% Sodium Chloride USP 2 mL injection N = 16	Overall N = 32
Age (years)	Mean (SD)	30.31 (7.03)	28.06 (5.72)	29.19 (6.41)
	Median	32.0	28.0	28.0
	Min, Max	19, 41	19, 41	19, 41
Gender				
Male	n (%)	11 (68.8)	11 (68.8)	22 (68.8)
Female	n (%)	5 (31.3)	5 (31.3)	10 (31.3)
Race				
Asian	n (%)	0	1 (6.3)	1 (3.1)
White	n (%)	10 (62.5)	6 (37.7)	16 (50.0)
Black/ African American	n (%)	6 (37.5)	9 (56.3)	15 (46.9)
Ethnicity				
Hispanic/ Latino	n (%)	12 (75.0)	8 (50.0)	20 (62.5)
Non-Hispanic/ Non-Latino	n (%)	4 (25.0)	8 (50.0)	12 (37.5)
BMI (kg/m^2)	Mean (SD)	27.36 (2.90)	27.20 (3.59)	27.28 (3.21)
	Median	27.55	27.45	27.45
	Min, Max	21.40, 33.00	21.70, 33.70	21.40, 33.70

Source: Applicant Clinical Study Report, Table 14.1.3

Reviewer Comments: The dose studied in the local irritation studied was appropriate and is the highest recommended dose for IV palonosetron. There were no patients (CINV or PONV) included in the local irritation study. This application is a 505(b)(2) and relies on the safety data of the RLD ALOXI®. Assessing phlebitis and local infiltration in healthy adult subjects is appropriate, as there is less confounding in these patients who are not receiving other IV medications concomitantly. The study was not statistically powered to detect a difference in phlebitis or infiltration, compared to sodium chloride, however, there was no safety signal observed, and the palonosetron product was well tolerated.

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

Reviewer Comments: This application is a 505(b)(2) and relies on the safety and efficacy data of the RLD, ALOXI® Injection. As such, the Applicant was not required to assess for potential adverse events related to the active ingredient, palonosetron. The formulation for this product differs from the approved product in that it does not contain a buffer or tonicity agent. Because of these formulation differences, the Applicant completed the clinical study described in order to assess the incidence of local irritation (phlebitis and infiltration) compared with local irritation of 0.9% Sodium Chloride Injection, USP. This reviewer does not believe the Applicant adequately addressed the potential for hemolysis, based on the hypotonic formulation of the proposed drug product.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during this study.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events during this study.

7.3.3 Dropouts and/or Discontinuations

Thirty-two healthy subjects were enrolled and received study treatment. All 32 subjects completed the study as planned. There were no dropouts and/or discontinuations due to adverse events.

Table 11: Subject Disposition

	Treatment		
	Palonosetron Hydrochloride 0.25mg/2mL Injection N = 16	0.9% Sodium Chloride Injection USP 2 mL N = 16	Overall N = 32
Subjects randomized	16 (100%)	16 (100%)	32 (100%)
Discontinued prematurely	0	0	0
Subjects completed	16 (100%)	16 (100%)	32 (100%)

Source: Applicant Clinical Study Report, Table 14.1.1

PROTOCOL DEVIATIONS:

There were 21 protocol deviations during the course of the trial. None of the protocol violations were considered major deviations, all patients met the inclusion/exclusion criteria at screening and Day 1, and no protocol violation led to exclusion from the safety population. Six (6) protocol violations were reported in 4 patients in the 0.9% Sodium Chloride Injection arm, and 15 protocol violations were reported in 7 patients in the Palonosetron Hydrochloride 0.25 mg/2mL arm. A listing of protocol violations by treatment group and subject number is provided in Table 12 below.

Table 12: Protocol Violations

Subject Number	Description of Deviation
0.9% Sodium Chloride Injection Treatment Group	
101	- Day 2, 24 hours post-dose ECG 58 minutes out of window
106	- 216 hour post-dose vital signs and skin assessments outside 60 minute window - 240 hour post-dose skin assessments outside 60 minute window
116	- 216 hour post-dose vital signs and skin assessments outside 60 minute window
124	- 72 hour post-dose vital signs and skin assessments outside 60 minute window - 144 hour post-dose vital signs outside 60 minute window
Palonosetron Hydrochloride 0.25mg/2mL	
108	- 168 hours post-dose vital signs and skin assessments outside 60 minute window - 192 hours post-dose vital signs and skin assessments outside 60 minute window - 240 hours post-dose vital signs and skin assessments outside 60 minute window
114	- Day 2, 24 hour post-dose ECG 54 minutes out of window
115	- 72 hours post-dose vital signs and skin assessments outside 60 minute window - 96 hours post-dose vital signs and skin assessments outside 60 minute window - 120 hours post-dose vital signs and skin assessments outside 60 minute window - 144 hours post-dose vital signs and skin assessments outside 60 minute window
121	- 72 hours post-dose vital signs outside 60 minute window - 192 hours post-dose vital signs and skin assessments outside 60 minute window - 216 hours post-dose vital signs and skin assessments outside 60 minute window - 240 hours post-dose vital signs and skin assessments outside 60 minute window
125	- 72 hours post-dose vital signs and skin assessments outside 60 minute window
127	- 192 hours post-dose vital signs and skin assessments outside 60 minute window
129	- 168 hours post-dose vital signs outside 60 minute window

Source: Listing 16.2.2.1 from Applicant Clinical Study Report.

Reviewer Comments: All subjects who were randomized completed the study and were included in the safety analysis population. The protocol violations were reviewed by this reviewer – although there was an imbalance in the number of protocol violations (15 vs 6 in the palonosetron arm and sodium chloride arm, respectively), this reviewer does not believe the protocol violations would impact the conclusions of this trial. Local irritation (i.e. phlebitis and infiltration) were not observed beyond 4 hours. All protocol violations were related to assessments made outside the time window, but these violations impacted assessments at 72-hours and beyond, well beyond the time frame in which local irritation was observed.

7.3.4 Significant Adverse Events

There were no significant adverse events during this study.

7.3.5 Submission Specific Primary Safety Concerns

The primary submission specific safety concerns addressed by the Applicant were related to the potential for local irritation due to differences in formulation between this product and the RLD. The primary outcome measures assessed the incidence of phlebitis and local infiltration at the IV site using the Phlebitis and Infiltration scale scoring described below. The other submission specific primary safety concern identified by this reviewer is hemolysis, due to the lack of a tonicity agent in the investigational product. Release specifications for the Applicant's proposed product include an osmolality of approximately 0 mOsm/kg. By comparison, the osmolality of the RLD is isotonic (290 – 305 mOsm/kg). The comparator in their pilot safety study was also isotonic (~300 mOsm/kg).

Phlebitis:
The IV site was assessed at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post dose, and the primary outcome compared the incidence rate of phlebitis cases expressed as a percentage of the exposed population. Odds ratios for the two groups were calculated with 95% CI.

Table 13: Phlebitis Scale

Skin Appearance	Score
No Symptoms	0
Erythema at access site with or without pain	1+
Pain at access site with erythema and/or edema	2+
Pain at access site with erythema and/or edema, streak formation, palpable venous cord	3+

Source: Applicant Protocol EPS-2014-001.

The maximum phlebitis scores observed were 1+, and no phlebitis was reported after the 4 hour time point in each treatment group. The mean (SD) of the maximum phlebitis score for Palonosetron Hydrochloride 0.25mg/2 mL was 0.3 (0.48) and for 0.9% Sodium Chloride was 0.2 (0.40). The difference between the two treatment arms was not statistically significant (0.4216). Overall there were 10 incidents of phlebitis score > 0 for Palonosetron Hydrochloride treated subjects and there were 4 incidents of phlebitis score > 0 for 0.9% Sodium Chloride treated subjects. The incidence rate of phlebitis per 100 people was calculated by treatment and time point through 4 hours post-dose. There was no additional phlebitis reported after 4 hours post-dose. The overall odds ratio calculated in this study reflects that the incidence of phlebitis with Palonosetron Hydrochloride injection was 1.97 times the odds of the incidence of phlebitis using 0.9% Sodium Chloride with a 95% confidence interval of (0.38, 10.17). These results are shown in **Table 14** below.

Table 14: Calculated Incidence Rate of Phlebitis[a] by Treatment Arm

Time Point	Incidence Rate		Odds Ratio	Odds Ratio 95% Confidence Interval
	Palonosetron Hydrochloride 0.25 mg/2mL Injection (N = 16)	0.9% Sodium Chloride Injection, USP, 2 mL (N = 16)		
Overall	31.3	18.8	1.97	(0.38, 10.17)
0.5 hour	18.8	12.5	1.62	(0.23, 11.26)
1.0 hour	12.5	6.3	2.14	(0.17, 26.33)
2.0 hour	6.3	0	3.19	(0.12, 84.43)
4.0 hour	25.0	6.3	5.00	(0.49, 50.83)

Source: Applicant's Clinical Study report, Table 14.2.1.3
[a] Phlebitis defined as a phlebitis score ≥ 1
[b] Incidence rate per 100 subjects
[c] Overall: subject with phlebitis at any time point
[d] There were zero cases of phlebitis after 4.0 hour timepoint

The maximum phlebitis score was 1 in either treatment group.

Infiltration:
The IV site was assessed at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post dose.

Table 15: Infiltration Scale

Skin Appearance	Score
No symptoms	0
Skin blanched, edema < 1 inch in any direction, cool to touch, with or without pain	1
Skin blanched, edema 1 to 6 inches in any direction, cool to touch, with or without pain	2
Skin blanched, translucent; gross edema > 6 inches in any direction; cool to touch; mild to moderate pain; possible numbness	3
Skin blanched, translucent; skin tight, leaking; skin discolored, bruised, swollen; gross edema > 6 inches in any direction; deep pitting tissue edema; circulatory impairment; moderate to severe pain; infiltration of any amount of blood product, irritant or vesicant	4

Source: Applicant Protocol EPS-2014-001.

The maximum infiltration score following intravenous injection of Palonosetron Hydrochloride was 1 reported at 0.5 and 1 hrs after injection. There were no reports after the 1 hour time point. The maximum infiltration score following intravenous injection of 0.9% Sodium Chloride was 1 at 0.5, 1, and 2 hours after injection. There were no reports after the 2 hour time point.

Hemolysis:

Hemolysis was not specifically identified by the Applicant as a submission specific safety concern. Symptoms of hemolysis include chest pain, dyspnea, abdominal pain, hypotension, burning pain, and fever. Lab abnormalities which may be seen with hemolysis include changes in hemoglobin, hematocrit and unconjugated bilirubin.

No adverse events were reported which are consistent with hemolysis. There were no clinically significant vital sign parameters noted during the study, however, vital signs were assessed at baseline (prior to infusion) and not again until 2 hours after infusion. Similarly, there were no clinically significant laboratory parameters; however, these were assessed only at baseline and Day 10.

Reviewer Comments: Skin reactions were evaluated by 2 independent observers and scored according to the following scales: There were no significant safety findings in the Applicant's pilot study; however, the sample size was quite small, making inferences difficult. The statistical "Rule of Three" states that, in a study where no events are observed, the 95% confidence upper bound for the true event rate is approximately 3/n, where n is the study sample size (or in this case, the total sample size exposed to palonosetron)(Jovanovic, B.D. and Levy, P.S. A Look at the Rule of Three. The American Statistician 1997;51(2):137-139). Using this principle, based on 0 cases of hemolysis with 16 patients exposed, the upper bound of 95% confidence interval (CI) of the risk estimate for hemolysis in palonosetron treated patients is 3/16 or approximately 19%. The rule of three is considered more accurate and is more commonly used with larger sample size.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 2 subjects experienced treatment emergent adverse events during the study, 1 from each treatment arm.

- Subject 107 receiving 0.9% Sodium Chloride injection experienced 2 AEs (nausea and diarrhea) following single dose administration,
- Subject 127 receiving Palonosetron Hydrochloride 0.25mg/2mL experienced constipation following single dose administration.

Both AEs were considered mild in intensity and resolved without complications.

Reviewer Comments: There were few AEs observed during this study, and there was no indication of increased AEs in the patients receiving palonosetron hydrochloride, however, only 16 patients received study drug. This number of patients should be sufficient only to observe at least 1 AE for any given AE which occurs at a rate of ~17% or more.

7.4.2 Laboratory Findings

No laboratory parameter findings were considered clinically significant.

Reviewer Comments: There were no significant changes in laboratory parameters, however, lab assessments occurred 10 days after infusion and would be expected to normalize by that time. Furthermore, labs relevant to a workup for hemolysis (lactate dehydrogenase, unconjugated bilirubin) were omitted from the assessment.

7.4.3 Vital Signs

Vital signs were assessed as described in 7.2 Adequacy of Safety Assessments. There were no clinically significant changes in vital signs during the study. A summary of blood pressures by treatment and select time points (baseline, 2, and 6 hours post-dose) is shown in **Table 16.**

Table 16: Summary of Blood Pressure by Treatment at Baseline, 2 and 6 Hours

Vital Sign (unit)	Visit	Statistics	Palonosetron hydrochloride 0.25 mg/2mL Injection (N = 16)	0.9% Sodium Chloride Injection, USP, 2mL (N = 16)
Systolic blood pressure	Baseline (pre-dose)	Mean (SD)	120.1 (13.62)	120.6 (16.65)
		Median	115.5	117.5
		Min, Max	104, 155	101, 169
	2 hours post-dose	Mean (SD)	114.3 (10.80)	115.0 (9.97)
		Median	112.5	114.0
		Min, Max	98, 139	103, 139
	Δ from baseline to 2 hrs	Mean (SD)	- 5.8 (12.58)	- 5.6 (8.76)
	6 hours post-dose	Mean (SD)	118.4 (11.45)	117.5 (12.13)
		Median	118.0	114.5
		Min, Max	102, 146	101, 140
	Δ from baseline to 6 hrs	Mean (SD)	- 1.8 (12.21)	- 3.1 (12.50)
Diastolic blood pressure	Baseline (pre-dose)	Mean (SD)	76.3 (8.01)	78.8 (7.08)
		Median	74.5	78.0
		Min, Max	62, 89	62, 88
	2 hours post-dose	Mean (SD)	72.6 (7.00)	75.9 (5.60)
		Median	71.5	76.5
		Min, Max	59, 86	67, 85
	Δ from baseline to 2 hrs	Mean (SD)	-3.7 (6.27)	-2.9 (4.51)
	6 hours post-dose	Mean (SD)	70.9 (6.67)	72.4 (7.54)
		Median	69.5	75.0
		Min, Max	62, 88	57, 84
	Δ from baseline to 6 hrs	Mean (SD)	-5.4 (6.77)	-6.4 (6.91

Source: Applicant's Clinical Study Report, Table 14.2.5

Reviewer Comments: There were no clinically relevant changes in any vital sign parameters. Vital signs were not captured until 2 hours post-dose, however, no AEs were reported (dizziness, headache) that might suggest changes in these parameters acutely following infusion.

7.4.4 Electrocardiograms (ECGs)

There were no clinically significant ECG parameters or ECG changes noted during the study.

7.4.5 Special Safety Studies/Clinical Trials

No additional safety studies were performed.

7.4.6 Immunogenicity

Palonosetron hydrochloride is not a therapeutic protein product, and no specific studies were performed to determine the immunogenicity of palonosetron.

7.5 Other Safety Explorations

N/A

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

N/A

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed.

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This application for Palonosetron Hydrochloride Injection does not contain a new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration and therefore does not trigger PREA. No pediatric assessment is required.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

N/A

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

The Applicant's proposed label was adopted from the RLD labeling (ALOXI®, NDA 21372). Labeling negotiations are ongoing at the time of this review.

9.3 Advisory Committee Meeting

There was no FDA Advisory Committee Meeting held for discussion of NDA 207963.

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/s/

LAURIE B MULDOWNEY
06/15/2015

JOYCE A KORVICK
06/15/2015