CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 29, 2008
To:	Donna Griebel, MD, Acting Director Division of Gastroenterology Products
Thru:	Kristina Arnwine, PharmD, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Bill Bender, RPh Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Aloxi Labeling Supplement
Drug Name(s):	Aloxi (Palonosetron HCL Injection)
Submission Number:	SE1-008 (b) (4) SE1-010
Application Type/Number:	NDA 21-372
Applicant/sponsor:	Helsinn Healthcare
OSE RCM #:	2008-232

CONTENTS

EXECUTIVE SUMMARY

DMETS' analysis of the container, carton and insert labeling noted improvements that should be made to the container label and carton labeling to decrease the potential for selection errors, mimimize confusion with dosing, and increase readability of information presented on the labeling. Such improvements include changing the color of the carton and the proprietary name for the 0.075 mg/1.5 mL strength to differentiate it from the color on the current 0.25 mg/5 mL strength. In addition, the proprietary name should be the same solid color on both the carton and container. For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Gastroenterology Products (DGP) to evaluate the container label and labeling supplement for Aloxi (palonosetron HCL) intravenous injection, 0.075 mg/1.5 mL (0.05 mg/mL) for the prevention of postoperative (b) (4) (b) (4) nausea and vomiting (PONV/PDNV) for up to (b) (4)

1.2 REGULATORY HISTORY

Aloxi was approved on July 25, 2003 and is currently indicated for: (1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and (2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Aloxi is currently supplied as a 0.25 mg/5 mL (0.05 mg/mL) single-use vial for intravenous injection.

1.3 PRODUCT INFORMATION

Aloxi (palanosetron HCL) is a 5-HT3 receptor antagonist with a strong binding affinity for this receptor and weak affinity for other receptors. Aloxi is currently indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy and for acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer therapy. The recommended dose for adults is a single 0.25 mg intravenous dose administered over thirty seconds approximately thirty minutes before the start of chemotherapy. The safety and effectiveness in patients below the age of 18 years has not been established.

The sponsor's proposed indication for Aloxi is the prevention of postoperative (b) (4) nausea and vomiting (PONV (b) (4) up to (b) (4) The dosage for adults is 0.075 mg administered as a single dose intravenously over ten seconds immediately before induction of anesthesia. Aloxi is not indicated for patients under the age of 18.

Aloxi will be available as 0.25 mg/5 mL (0.05 mg/mL) and 0.075 mg/1.5 mL (0.05 mg/mL) single-use intravenous vials. Aloxi is stored at room temperature (20°C-25°C) and should be protected from light.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including the proprietary and established name, strength, form, container quantity, expiration date, and so on. The insert labeling is intended to communicate to practitioners all the information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program (MERP) may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

DMETS staff analyzes reported misuse of drugs and are able to use their experience to identify potential errors with all packaged, labeled and/or prescribed medications. DMETS uses failure mode and effects analysis (FMEA) and human factor principles to identify potential sources of error with the proposed product labels and insert labeling. DMETS then provides recommendations that aim at reducing the risk of medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM

Because Aloxi has been marketed since 2003, DMETS conducted a search of the Adverse Event Reporting System (AERS) database to determine if any medication errors are associated with the use of Aloxi. The MedDRA Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Medication Errors Due to Accidental Exposures", "Medication Monitoring Errors", and the Preferred Terms (PT) "Overdose", "Accidental Overdose", "Multiple Drug Overdose", "Multiple Drug Overdose Accidental", and verbatim substance names "Alox%" and "Palonos", tradename "Aloxi", and active ingredient "Palonosetron" were used as search criteria.

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. DMETS reviewed the cases within each category to identify factors that contributed to the medication errors.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

2.2 LABELS AND LABELING

For this product, the Sponsor submitted on October 10, 2007, the following labels and insert labeling for DMETS review (see Appendices A and B for images):

- Container Label: 0.075 mg/1.5 mL (0.05 mg/mL) vial
- Carton Labeling: 0.075 mg/1.5 mL (0.05 mg/mL) vial
- Prescribing Information- package insert and patient package insert (no image)

Additionally, the Sponsor provided the current carton labels for comparison (see Appendices C and D for images):

- Current Container Label: 0.25 mg/5 mL (0.05 mg/mL) vial
- Current Carton Labeling: 0.25 mg/5 mL (0.05 mg/mL) vial

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The FDA Adverse Event Reporting System (AERS) search conducted on February 26, 2008, yielded two cases involving Aloxi. Of the two cases, one was determined to involve a medication error in which the patient received an extra dose of Aloxi without any adverse effects as a result of the extra dose. No causality was included as to why the patient was administered the second dose in error. The second case only listed Aloxi as a concomitant medication but did not involve Aloxi in the medication error.

3.2 CONTAINER LABEL

Review of the container labels and carton labeling identified several potential sources of medication errors. These concerns are noted below.

The color scheme of the proposed 0.075 mg/1.5 mL vial (b) (4) (b) (4) and the currently marketed 0.25 mg/5 mL vial (b) (4) (b) (4) appear to be very similar and are virtually indistinguishable.

The product strength (b) (4) however the established name (b) (4)

Two different color fonts (b) (4) in the proprietary name.

The (b) (4) or the established name and product strength does not provide adequate contrast.

The established name appears to be smaller (b) (4) trade name (b) (4) (b) (4)

The product strength lacks prominence and is difficult to read.

The (b) (4) utilized for the NDC number, distributor statement, and storage recommendations makes the information difficult to read.

3.3 CARTON LABELING

The product strength is expressed (b) (4) however the established name (b) (4)

Two different color fonts (b) (4) in the proprietary name.

The large (b) (4) graphic makes the label difficult to read.

The (b) (4) gray background utilized for the established name and product strength does not provide adequate contrast.

The established name (b) (4) trade name (b) (4) (b) (4)

The product strength lacks prominence and is difficult to read.

(b) (4) (b) (4) has a trailing zero.

The (b) (4) side panels makes the information presented therein difficult to read.

3.4 INSERT LABELING

The abbreviation "IV" is used for the word intravenous or intravenously throughout the physician labeling.

The heading in the Dosage and Administration section of the package insert entitled (b) (4)

4 DISCUSSION

Our analysis of the container labels and carton labeling noted areas of vulnerability that could lead to medication errors. For example, the proposed color scheme on the container label for the 0.075 mg/1.5 mL strength (b) (4) is very similar to the currently marketed 0.25 mg/5 mL strength (b) (4). Our postmarketing experience demonstrates that product selection errors may occur due to the similar appearance of container labels especially when similar colors and trade dress are used. Selection errors may be perpetuated during administration leading to overdose and potentially resulting in adverse events.

We also noted the use of two different colo (b) (4) in the proprietary name on the container label and carton labeling. The (b) (4) name is distracting and promotional as it appears to be a (b) (4) The use of two different color fonts may cause the name to be misinterpreted as (b) (4), letter. Furthermore, the applicant (b) (4) to the proposed carton labeling. (b) (4) on the grey background utilized for the established name, product strength, route of administration, and net quantity does not provide adequate contrast. Poor color contrast leads to low legibility and often misinterpretation. Additionally, due to the color scheme and font type of the trade name, (b) (4) (b) (4) The letters comprising the established name should be presented with prominence commensurate to that of the proprietary name. All pertinent factors, including, typography, layout, contrast, and other printing features should be taken into account in accordance with 21 CFR 201.10(g)(2).

DMETS also noted that the product strength is expressed (b) (4) however; the established name (b) (4) (b) (4) (b) (4) Additionally, the product strength is small making it difficult to locate. Since there will be two Aloxi products on the market, it is important that the strengths are readily distinguishable in order to minimize the potential for selection errors.

We also noted the heading in the Dosage and Administration section of the package insert entitled (b) (4) (b) (4) (b) (4) We are also concerned with the use of a trailing zero on the carton labeling and the abbreviation "IV" in the package insert. Trailing zeros are considered dangerous abbreviations and are listed on the Institute for Safe Medication Practices (ISMP) "List of Error-Prone Abbreviations, Symbols, and Dose Designations". The decimal place is often not seen when trailing zeros are used. (b) (4) (b) (4) We also noted the use of the abbreviation "IV". "IV" could potentially be misinterpreted for another route of administration (e.g. IM) or a dosage unit (e.g. IU) and lead to medication errors. In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations such as "IV" and trailing zeros in prescribing. As part of this campaign, FDA agreed not to approve such abbreviations in their labeling because these abbreviations are carried on to the prescribing practice.

The approval of this application will allow for one additional strength of Aloxi (0.075 mg/ 1.5 mL). It does not appear that this additional strength poses any dosing problems but the labels and labeling for this new strength should be adequately distinguished from the currently marketed product to avoid selection errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The approval of the new 0.075 mg/1.5 mL strength does not appear to increase the risk of medication errors. However, efforts need to be made to adequately differentiate the visual similarity of this new strength from the currently marketed strength.

DMETS recommends the label and labeling recommendations outlined below be implemented to improve differentiation between the differing strengths and to increase readability of the labels and labeling,

DMETS would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-2084.

5.1 COMMENTS TO THE DIVISION

The heading in the Dosage and Administration section of the package insert entitled (b) (4)

The comments below should be forwarded to the applicant so that these recommendations can be implemented prior to approval of this supplement.

Based upon our assessment of the labels and labeling, DMETS has identified areas of needed improvement. We have provided recommendations in section 5.2 below and request this information be forwarded to the applicant.

5.2 COMMENTS TO THE APPLICANT

A. Container Label

1. Revise the established name and product strength so that they are in accordance (b) (4) Consult Rik Lostritto, chair of the CDER Labeling and Nomenclature Committee for further guidance.
2. Revise the color scheme for the 0.075 mg/1.5 mL strength to ensure it is adequately differentiated from the 0.25 mg/5 mL strength.
3. Revise the color scheme for the proprietary name so that the entire name is presented in one color font.
4. Revise the color of the font utilized for the established name and product strength so that it provides adequate contrast against the grey backround.
5. Increase the prominence of the established name and product strength.

B. Carton Labeling

1. Revise the established name and product strength so that they are in accordance with (b) (4) Consult Rik Lostritto, chair of the CDER Labeling and Nomenclature Committee for further guidance.
2. Revise the color scheme of the proprietary name so that the entire name is presented in one color font.
3. Revise the color of the font utilized or the established name and product strength so that it provides adequate contrast against the grey backround.
4. Increase the prominence of the established name and product strength.
5. Eliminate the use of trailing zeroes.
6. Include a "New Strength" banner on the principal display panel for a period not to exceed six months.

C. Insert Labeling

1. Eliminate the use of the abbreviation "IV". Revise all references to read "intravenously" or "intravenous".

12.3 Pharmacokinetics

- [redacted] (b) (4)

  We suggest revising this sentence slightly for clarity. We recommend,

  > After intravenous dosing of palonosetron in patients undergoing surgery (abdominal surgery or vaginal hysterectomy), the pharmacokinetic characteristics…"

- We suggest that the subsections for Distribution, Metabolism, etc. not be indented. Indenting makes them appear that they belong under the PONV paragraph that precedes them.

14 Clinical Studies

- Because this drug will now have two distinct indications, we suggest that section 14.1 be for the CINV studies and 14.2 for PONV.

- We will defer comments on the PONV clinical study description until an updated version of the label is available.

17 Patient Counseling Information

- The first line, "See FDA-approved Patient Labeling (17.2)" should not [redacted] (b) (4) (but should remain italicized).

17.2 FDA-Approved Patient Labeling

- Although the patient labeling is not the subject of this review, please ensure that all mention of [redacted] (b) (4) is deleted.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

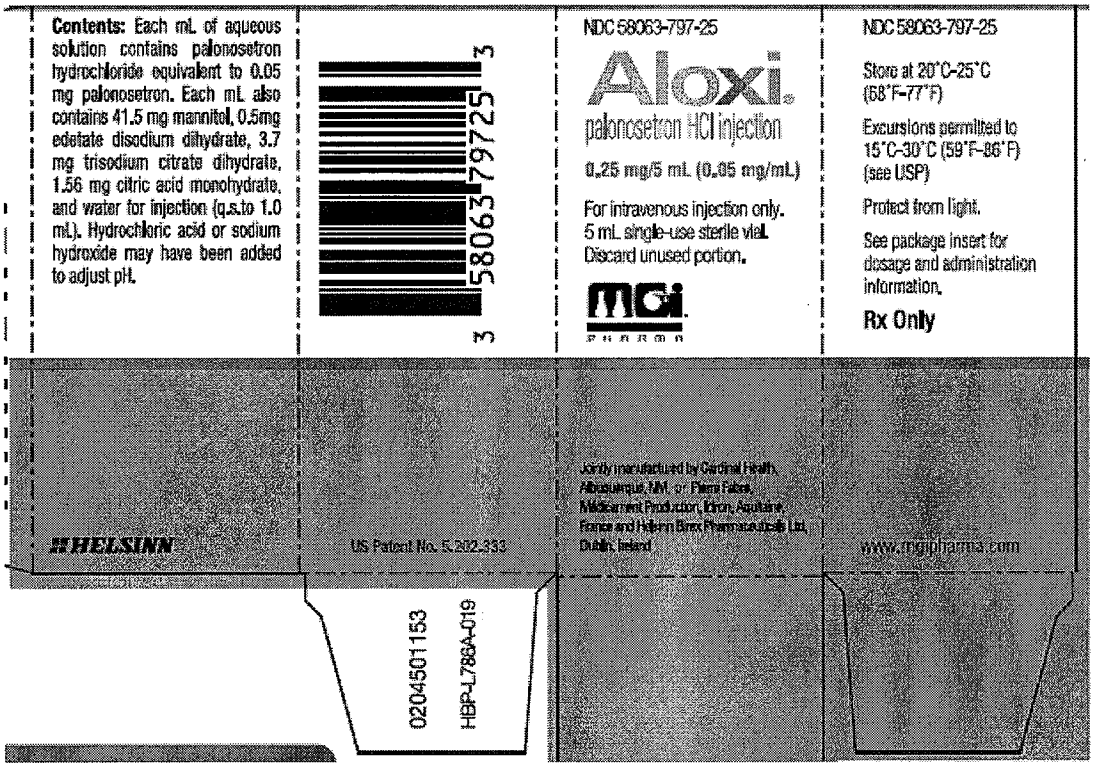
Appendix C: Currently Marketed Container Label 0.25 mg/mL

*PMS Colours to be listed on each film (beside or on top of the Proof Image)

Tel: + 353 (0) 1 822 5404 Fax: + 353 (0) 1 822 5410			HELSINN BIREX PHARMACEUTICALS LTD,			Damastown, Mulhuddart, Dublin 15	
Customer : HBT Ireland				**Customer Approval :**		**Date :**	
HPB :	# 0201101166	**# of colours :** 3		**HBPApproval :**		**Date :**	
Proof :	# 2	**Proof Date :** 21/6/07		**Proofed by : PAUL**		**Date : 21/6/07**	
Printer Part :	# 79333	**Varnish free area :** N/A		**Verified by : RORY**		**Date : 21/6/07**	
Design Description : USA MGI ALOXI VIAL LABEL			**Cutter Ref # :**			**Die Size :** 20 X 65	
TS :	# TS073	**Reel Width :** N/A	**Design Repeat :** N/A			**Design Width :** N/A	
Pharmacode :	#	**Glue Flap # :** N/A	**Barcode # :** RSS CODE			**Barcode Type :** N/A	
Pantone Matching System (PMS Colours) : Black P 158 P 652						**Unwind Direction :** N/A	
Guysal IDA Ind. Est. Ovens, Co.Cork			Tel: + 353 21 850650		Fax: + 353 21 850699	**PO #:** 79333	
Holfeld Graphics			Tel: + 353 1 2855233		Fax: + 353 1 2853061	**Printer #:** 07-2955	

Please check proof carefully, while every effort has been taken to ensure it is correct, when you are satisfied please sign above and return.

Appendix D: Currently Marketed Carton Labeling 0.25 mg/mL



Please complete the necessary areas marked: X within this checkbox.
Failure to do so will mean this approval will be returned for completion.

FIELD BOXMORE
HEALTHCARE PACKAGING
Enterprise Way, Highfield Industrial Estate, Newtownabbey, Northern Ireland, BT36 4HW.
Tel: +44 (0) 28 9083 4000 Fax: +44 (0) 28 9083 4000 Intl: +44 (0) 28 9083 4004
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Customer	Helsinn birex
Job Description	USA MGI Aloxi carton
Customer Spec. No.	N/A
Customer Ref.	0204501153
Keyline Ref:	L786A
Glue Flap Code	18 (12 digit)
Proof Number	2
Proof Date:	7/11/05
Proofed By:	KW
Verified By:	
Filed @ Esko	
Filed @ ArtPro	hel-0204501153
Size	33 x 32 x 71mm
Pharma Code Edge Code	806
Barcode 1 & Number	tbc
Barcode 2 & Number	n/a
Paper/Board Type & Caliper	TBC
Leaflet Folding Details	n/a
Label Edge Leading	n/a

What type of varnish is required?
If none is specified, WATER BASED varnish will be used!

Please Indicate/verify Varnish Free Areas that you require.
If none are specified, an ALL-OVER varnish will be applied!

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INKS / COATINGS / EFFECTS	PRINTING Front	Back
Black	✓	
PMS 158	✓	
PMS 652	✓	
Varnish Free Area		
Keyline		

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