

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-233**

**OTHER REVIEW(S)**

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: August 19, 2008

FROM: Hyojong Kwon, Ph.D.  
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. \_\_\_\_\_  
Associate Director - Bioequivalence  
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-233,  
Aloxi (palonosetron hydrochloride) 0.5 mg Oral  
Capsule, Sponsored by Helsinn Healthcare SA

TO: Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products (DGP)

At the request of DGP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** PALO-06-16

**Study Title:** "Bioequivalence of a single oral dose of two formulations (Formulation A and Formulation B) of palonosetron 0.5 mg softgel capsule in healthy male and female subjects. (A two treatments, two periods, two sequences, open label, randomized, cross-over study)"

The clinical and analytical portions of the study were conducted at \_\_\_\_\_ (b) (4)

\_\_\_\_\_,  
respectively.

Following the inspections at \_\_\_\_\_ (b) (4)  
\_\_\_\_\_, a Form 483 was issued. The objectionable items and our evaluation of them follow:

**Clinical Site:**

(b) (4)

No 483 observation

**Analytical Site:**

(b) (4)

**Analytical observations for Study PALO-06-16:**

- 1) **Quality control samples (QCs) for palonosetron, M9 and M4 are not representative of actual sample values.**

Please refer to the following tables:

<b>Palonosetron</b>		<b>M9</b>		<b>M4</b>	
<b>QCs</b>	<b>ng/L</b>	<b>QCs</b>	<b>ng/L</b>	<b>QCs</b>	<b>ng/L</b>
Low QC	111.06	Low QC	27.73	Low QC	127.16
Mid QC	1075.45	Mid QC	268.52	Mid QC	1231.35
High QC	1729.16	High QC	431.73	High QC	1979.81
<b>Cmax</b>	<b>ng/L</b>	<b>Cmax</b>	<b>ng/L</b>	<b>Cmax</b>	<b>ng/L</b>
Lowest Cmax	463.86	Lowest Cmax	49.28	Lowest Cmax	51.2
Highest Cmax	1322.77	Highest Cmax	251.35	Highest Cmax	130.79

Although the QC values for palonosetron were not optimal, the QC performance in accepted runs was acceptable and the low and mid QCs were relevant to the observed subject sample concentrations. For M9, all observed Cmax values fell below the mid QC. For M4, all observed Cmax values were at or below the low QC. Although the high QC for M9 and the mid and high QCs for M4 were not reflective of concentrations observed in the subject samples, it is recognized that the M9 and M4 metabolites are not primary endpoints for the bioequivalence determination. For future studies, the firm should utilize a calibration range and QC levels appropriate to the study.

- 2) **There is no supportive study or information to verify that the concentration of M9 does not interfere with the concentrations of palonosetron in plasma. In the stability studies during validation, palonosetron and M9 were evaluated together in plasma. Therefore, backconversion of M9 and palonosetron can not be detected.**

For the stability experiments and during study conduct, the firm used QCs and calibration standards that were spiked with all three analytes (palonosetron, M9, and M4); the analyte concentrations were measured simultaneously with a multi-analyte method. Although back-conversion of M9 (the N-oxide metabolite) to palonosetron is possible, this design could not have detected conversion of M9 to palonosetron. The firm should have evaluated the extent of M9 conversion and its impact on the accuracy of palonosetron concentration measurements. (For example, the firm could have spiked plasma with M9 only and measured palonosetron.)

- 3) During M4 validation study# PALO-04-03, validation runs for matrix effect, M4 stability at ambient temperature for 24 hrs, and M4 autosampler stability at 4°C for 22 days failed to meet a priori run acceptance criteria.**

The firm accepted the results from the evaluation of the matrix effect, ambient temperature stability and autosampler stability, although the results fell outside the acceptance criteria (>15% CV for QCs spiked in plasma from various donors, or >15% loss during storage) specified in the firm's SOP. In spite of the failed validation runs, the firm used the method for M4 analysis without further investigation or changes to the method.

- 4) There was no expiration date on the Certificate of Analysis for the M4 reference standard used in validation study# PALO-04-03 and BE study# PALO-06-16.**

The firm was unable to provide supportive documentation specifying the expiration date of the M4 standard, since the CoA did not have that information. The firm stated that they had difficulty obtaining the M4 reference standard; [REDACTED] (b) (4) [REDACTED]

**Additional Inspectional Finding:** The firm's practice regarding incurred sample reanalysis (ISR) states that reanalysis of test samples to demonstrate the reproducibility of the method will be conducted according to the recommendations of the study plan, based on the sponsor's request. The firm was advised to specify acceptance criteria and define the minimum number or percentage of study samples that will be reanalyzed.

**Conclusion:**

Following the above inspections, the Division of Scientific Investigations recommends accepting the clinical and palonosetron pharmacokinetic data from Study PALO-06-16.

**After you have reviewed this transmittal memo, please append it to the original NDA submission.**

Hyojong Kwon, Ph.D.

**Final Classifications:**

**NAI:** [REDACTED] (b) (4)

**VAI:** [REDACTED] (b) (4)

cc:

OC DSI/RF

OC DSI/Vaccari

OC DSI/Kwon/CF

OND ODE3 DGP/Grewal

HFR-NE250/Noe

Draft: HK 8/18/08

Edits: JAO 8/18/08, 8/19/08; JAK 8/19/08; MFS 8/19/08

[REDACTED] (b) (4) O:\BE\EIRCOVER\22233hel.pal.doc

[REDACTED] (b) (4)

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

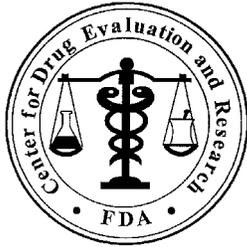
/s/

-----  
John Kadavil

8/19/2008 05:22:51 PM

PHARMACOLOGIST

Dr. Skelly (Acting for Dr. Viswanathan) signed the paper  
copy on 8/19/08. Dr. Kadavil signed for Dr.  
Kwon on 8/19/08.



**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: August 1, 2008

To: Donna Griebel, MD  
Director, Division of Gastroenterology Products, HFD-180

Through: Kellie Taylor, Pharm D, MPH, Team Leader  
Denise Toyer, Pharm D, Deputy Director  
Division of Medication Error Prevention and Analysis, HFD-420

From: Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis, HFD-420

Subject: Label and Labeling Review for Aloxi

Drug Name(s): Aloxi (palonosetron HCL) 0.5 mg capsules

Application Type/Number: NDA # 22-233

Applicant/sponsor: Helsinn Healthcare SA

OSE RCM #: 2008-965

## **CONTENTS**

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	3
1.1 Introduction .....	3
1.2 Product Information .....	3
2 METHODS AND MATERIALS .....	3
3 RESULTS .....	4
4 DISCUSSION .....	4
4.1 Labels and Labeling .....	4
4.2 Carton labeling .....	5
5 CONCLUSIONS AND RECOMMENDATIONS .....	6
5.1 Comments to the Division .....	6
5.2 Comments to the Applicant .....	6
6 REFERENCES .....	7
APPENDICES .....	8

## **EXECUTIVE SUMMARY**

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton labeling and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

### **1 BACKGROUND**

#### **1.1 INTRODUCTION**

This review is in response to a request from the Division of Gastroenterology Products to review the labels and labeling for the proposed proprietary name, Aloxi, (palonosetron HCl) 0.5 mg capsules for their potential to lead to medication errors.

#### **1.2 PRODUCT INFORMATION**

Aloxi (palonosetron HCl) capsules is a serotonin 5-HT<sub>3</sub> antagonist indicated the prevention of acute (b) (4) (b) (4) nausea and vomiting associated with moderately emetogenic chemotherapy. The 0.5 mg capsule represents a new dosage form, new strength, and new route of administration for palonosetron HCl. One capsule is taken orally one hour prior to the start of chemotherapy without regard to food. Aloxi is packaged in bottles containing five capsules and is stored at room temperature.

### **2 METHODS AND MATERIALS**

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis 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.<sup>1</sup>

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 proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all 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

---

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

Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because our staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The medication error prevention staff uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on June 10, 2008 the following labels and insert labeling for medication error prevention review (see Appendix A and B):

- Container label: 0.5 mg (5 capsules)
- Carton Labeling: 0.5 mg (5 capsules)
- Prescribing Information (no image)

### **3 RESULTS**

Upon review of the labels and labeling, the Division of Medication Error Prevention and Analysis noted several vulnerabilities that may contribute to medication errors.

The Applicant uses two colors of font in the presentation of the letter ‘x’ in the proprietary name, Aloxi.

The font of the established name appears to be at less than one half the size of the proprietary name on the carton labeling and lacks the prominence commensurate with the prominence with which the proprietary name appears.

The “Rx Only” statement appears on the back panel of the carton labeling.

The net quantity of capsules appears adjacent to the strength in a similar size font on the container labels and carton labeling.

The strength of the capsules is presented throughout the labels and labeling as 0.50 mg, using a trailing zero.

### **4 DISCUSSION**

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors.

#### **4.1 CARTON LABELING AND CONTAINER LABELS**

The use of two colors (blue and yellow) in the presentation of the proprietary name may affect its readability.

---

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

The font sizes of the strength of the product and the net quantity are similar and in close proximity to each other. The Institute for Safe Medication Practices (ISMP) identified this presentation as a contributing factor to medication errors.<sup>3</sup> The ISMP describes how the presentation of the strength and the net quantity in the same line can lead to the net quantity being confused as the strength (i.e, 5 mg rather than 0.5 mg). In addition, post-marketing surveillance demonstrates that the strength followed immediately by the net quantity as seen on the carton labels results in the patients believing the entire net quantity is required to achieve the desired dose. With the current presentation, we believe there is potential for healthcare providers or patients to mistakenly believe that five capsules are needed to produce the 0.5 mg dose of palonosetron.

#### **4.2 CARTON LABELING**

The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). The legibility of the established name is important for pharmacies to identify the active ingredient.

The carton label presents the “Rx Only” statement on the back panel. This statement assists pharmacy staff in identifying products as prescription rather than over-the-counter.

#### **4.3 INSERT LABELING**

Trailing zeros, an error prone dose designation<sup>4</sup>, appear throughout the labels and labeling. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, or symbols including trailing zeroes. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling. In general, this error-prone abbreviation creates the potential for a ten-fold dosing error when this abbreviation is carried over to prescribing and the decimal point is not readily apparent on a prescription. In this case, we believe the trailing zero adds to the potential confusion of this product with Adoxa 50 mg tablets as 0.50 mg looks more similar to this strength compared to 0.5 mg. Additionally, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2008 National Patient Safety Goals of The Joint Commission.<sup>5</sup>

---

<sup>3</sup> Institute for Safe Medication Practices, ISMP Medication Safety Alert, Vol. 6, Issue 23; Nov. 14, 2001.

<sup>4</sup> [www.ismp.org](http://www.ismp.org), “ISMP’s List of Error Prone Abbreviations, Symbols, and Dose Designations,” The Institute of Safe Medication Practices, 2006.

<sup>5</sup> [www.jointcommission.org](http://www.jointcommission.org), Official Do Not Use List, The Joint Commission, 2008.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Sponsor to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

### **5.1 COMMENTS TO THE DIVISION**

Eliminate the use of trailing zeroes, an error prone designation, throughout the labels and labeling of products. The Agency launched a campaign on June 14, 2006, warning healthcare practitioners and consumers not to use error prone abbreviations, acronyms, or symbols including trailing zeroes. As part of the campaign, FDA agreed not to use such error prone designations in their approved product labeling.

The medication error prevention staff provides recommendations in Section 5.2 that aim to reduce the risk of medication errors associated with the labels and labeling. We request these comments be forwarded to the Applicant.

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

### **5.2 COMMENTS TO THE APPLICANT**

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed has provided recommendations below for consideration.

#### **5.2.1 General Comments**

1. Revise the presentation of the proprietary name to include the use of only one color of font.
2. Eliminate the use of trailing zeroes, an error prone designation, throughout the labels and labeling. Present the capsule strength as 0.5 mg.

### **5.2.2 Container Label**

1. Revise the presentation of the proprietary name to include the use of only one color of font.
2. Separate the net quantity of the container from the strength of the product by moving the net quantity of capsules to the upper or lower edge of the label.
3. Prominently display the strength beneath the proprietary and established names.

### **5.2.3 Carton Labeling**

1. Revise the presentation of the proprietary name to include the use of only one color of font.
2. Revise the font of the established name so that it is at least one half the proprietary name and provides the prominence commensurate with the prominence with which the proprietary name appears per 21 CFR 201.10 (g)(2).
3. Place the “Rx Only” statement on the primary display panel.
4. Separate the net quantity of the container from the strength of the product by moving the net quantity of capsules to the upper or lower edge of the labeling.
5. Prominently display the strength beneath the proprietary and established names.

### **5.2.4 Insert Labeling**

1. Eliminate the use of trailing zeroes, an error prone designation, throughout the labels and labeling. Present the capsule strength as 0.5 mg.

## **6 REFERENCES**

1. OSE Review #2007-2522, Proprietary name review for Aloxi, Abate, R,

1 PAGE WITHHELD IN FULL IMMEDIATELY AFTER THIS PAGE AS (B)(4) DRAFT LABELING

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

/s/

-----  
Kellie Taylor  
8/1/2008 10:37:14 AM  
DRUG SAFETY OFFICE REVIEWER  
on behalf of R. Abate also

Denise Toyer  
8/4/2008 10:47:01 AM  
DRUG SAFETY OFFICE REVIEWER



**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: July 31, 2008

To: Donna Griebel, M. D., Director  
Division of Gastroenterology Products

Through: Jodi Duckhorn, M.A., Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Product Information Specialist  
**Patient Labeling and Education Team  
Division of Risk Management (DRISK)**

Subject: Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Aloxi (palonosetron HCl) Capsules

Application Type/Number: NDA 22-233

Applicant/sponsor: Helsinn Healthcare

OSE RCM #: 2007-2522

## 1 INTRODUCTION

Helsinn Healthcare received original approval for Aloxi (palonosetron HCl) for injection, NDA 21-372 on July 25, 2007. Helsinn Healthcare submitted an original New Drug Application, NDA 22-233 for Aloxi (palonosetron HCl) Capsules, on October 22, 2007. Aloxi (palonosetron HCl) Capsules are indicated for: Moderately emetogenic cancer chemotherapy-prevention of acute (b) (4) nausea and vomiting associated with initial and repeat courses. The sponsor's original submission includes proposed Professional Information in PLR format with proposed patient labeling in the form of a Patient Package Insert (PPI) in section 17.2 FDA-Approved Patient Labeling. The review division requested a review of the patient labeling submitted for this NDA. This review is written in response to that request.

## 2 MATERIAL REVIEWED

- ALOXI Professional Information submitted by the sponsor on October 22, 2007, and further revised by the Review division on July 22, 2008
- ALOXI Patient Package Insert (PPI) submitted by the sponsor on October 22, 2007, and further revised by the Review division on July 22, 2008
- Memorandum re: Review of ODS recommendations for revised labeling for Aloxi (palonosetron HCL injection, NDA #21-372) to include the adverse events of hypersensitivity/anaphylaxis, dated July 28, 2005 by Dr. Ann Marie Trentacosti, M.D.

## 3 DISCUSSION

The purpose of patient information leaflets is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.9, and a Flesch Reading Ease score of 55.9%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). Our revised PPI has a Flesch Kinkaid grade level of 7.6 and a Flesch Reading Ease score of 59.0%.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- made the PPI consistent with the PI,
- rearranged information as needed due to PLR formatting of the proposed PI
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question-and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with

low vision. We have reformatted the PPI document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

1. The Review Division should consult the Safety Requirements Team as soon as possible to determine if this new PPI for Aloxi will result in the need for a Risk Evaluation and Mitigation Strategy.
2. A PPI for TRADENAME is voluntary. Aloxi is supplied five capsules per bottle, each bottle packaged in a small carton. Unless Aloxi is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The Sponsor should state their mechanism for intended distribution of the PPI to patients.
3. The title of some proposed sections of the PPI includes the term “Aloxi Capsules” while others include only “Aloxi.” The sponsor should use one term consistently throughout the PPI.
4. We deleted the section (b) (4). This information is already contained in the section “What is Aloxi?” and reflects the labeled indication.

In the “What is Aloxi?” section we added the statement: “It is not known if Aloxi is safe and effective in people under the age of 18 years.

5. In the section “What should I tell my doctor before taking Aloxi?” we added the following bullet:
  - “have had an allergic reaction to another medicine for nausea or vomiting, such as Kytril (granisetron), Anzamet (dolasetron), Zofran (ondansetron), or to the medicine Lotronex (alosetron).”

The proposed PPI does not adequately address the issue of hypersensitivity to other 5HT<sub>3</sub> antagonists as it relates to the possibility of hypersensitivity reactions to Aloxi.

We revised the pregnancy and breast-feeding bullets to better reflect the PI language.

6. We expanded the section “How should I use Aloxi?” to include:
  - a statement that Aloxi may be taken with or without food
  - an instruction for patients to call their doctor right away if they take too much Aloxi
  - an instruction to follow their doctor’s instructions if they do not get enough relief of nausea and vomiting with Aloxi.
7. Serious side effects should be listed before common side effects in the section “What are the possible side effects of Aloxi?” We added “Serious allergic reactions” at the beginning of this section. The sponsor should include information in the PI regarding the types of hypersensitivity reactions that have been seen, and what patients should

report. Reportable signs and symptoms should be listed in this section of the PPI to inform patients what to look for and to do in the event of a hypersensitivity reaction, for example “Tell your doctor if you have any of the following signs or symptoms of a serious allergic reaction with Aloxi.”

8. We added the following statement to the end of the section, “General Information about Aloxi”:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Aloxi, we recommend adding this language to all FDA-approved patient labeling for consistency.

9. We added storage information consistent with the information in the PI.
10. Consider whether information should be added to the PPI for the IV formulation. PPIs are for the product, not a particular formulation or presentation.

Please let us know if you have any questions

6 PAGES WITHHELD IN FULL IMMEDIATELY AFTER THIS PAGE AS (B)(4) DRAFT LABELING

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

/s/  
-----

Sharon Mills  
7/31/2008 10:45:31 AM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
7/31/2008 11:14:32 AM  
DRUG SAFETY OFFICE REVIEWER