CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-372 SUPPL # S-008/ (b) (4) HFD # 180

Trade Name Aloxi

Generic Name Palonosetron Hydrochloride

Applicant Name Helsinn Healthcare SA

Approval Date, If Known N/A

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

S-008 (SE1) (b) (4) - both are 505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-372 Aloxi (palonosetron hydrochloride) 0.25 mg I.V.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

(b) (4)

S-008

Investigation #1: PALO-04-06 (Phase 3 trial - pivitol investigation)
Investigation #2: PALO-04-07 (Phase3 trial - confirmatory study)
Study 2500 (Phase 2 trial confirmatory study)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

S-008/ (b) (4)
Investigation #1: PALO-04-06 (Phase 3 trial - pivitol investigation)
Investigation #2: PALO-04-07 (Phase3 trial - confirmatory study)
Study 2500 (Phase 2 trial confirmatory study

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 39,797 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 39,797 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Jagjit Grewal
Title: Regulatory Project Manager
Date: 2/26/08

Name of Office/Division Director signing form: Joyce Korvick
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Jagjit S Grewal
2/29/2008 06:37:42 PM
CSO

Joyce Korvick
2/29/2008 07:38:22 PM
MEDICAL OFFICER

Pediatric Research and Equity Act Deferrals

Product name and active ingredient/ dosage form: **Aloxi** (palonosetron hydrochloride) Intravenous Injection, 0.075 mg/1.5 mL

NDA #: NDA 21-372 Supplement Type: SE1 – new indication (S008, (b) (4) SE8 – labeling w/clinical change (S010)

Supplement Numbers: S-008, (b) (4) S-010

HFD-180

Indication(s): Two new indications
(NOTE: If the drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

- Indication #1 (**S-008**): Aloxi is indicated for the prevention of post operative nausea and vomiting (PONV) for up to (b) (4)

1. Deferral specifics
   a. Pediatric age group(s) included in deferral: 1 month to 16 years old

   b. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
      - ☒ Adult studies completed and ready for approval
      - ☐ Additional safety or effectiveness data needed (**describe**)
      - ☐ Other (**specify**)

   c. Pediatric age group(s) not included in deferral: 0 months to 1 month old

   d. Reason(s) for not including the pediatric age group(s) listed in letter c in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
      - ☐ Adequate pediatric labeling exists
      - ☐ Studies completed in the specified age group
      - ☒ Requesting a partial waiver
      - ☐ Other (**specify**)

   2. The law requires that certain criteria be met BEFORE a deferral is granted. the applicant must submit—
      "(I) certification of the grounds for deferring the assessments;
      "(II) a description of the planned or ongoing studies;
      "(III) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; **and**
      "(IV) a timeline for the completion of such studies.

Has the Sponsor submitted these (if yes, this should be reviewed at the same time as the deferral). Yes, pediatric plan submission dated November 2, 2007

3. Has a pediatric plan been submitted to the Agency? Note: Pediatric plans MUST be reviewed by the Pediatric Review Committee (PeRC)
   - If so, provide date
     Submission dated November 2, 2007
   - If not, provided projected date pediatric plan is to be submitted

3. Timeline for the completion of studies
   December 13, 2008

4. Has a Written Request been issued?
   No

(b) (4)

(b) (4)

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/s/

Jagjit S Grewal
2/26/2008 11:38:12 AM
CSO

PeRC Pediatric Plan Template

Note: This table contains instructions to assist the division when completing this form (italicized text). ***Please remove the italicized text prior to sending the completed table to the PeRC.*** **.**

When completing the table, each section is intended to reflect elements considered important by the PeRC. When filling out the section, please insert what the Sponsor is proposing. Some elements may not be applicable, or there may be other important issues that the Division wishes to discuss. Please add items that you believe are necessary. If an element is not applicable, please write "NA" rather than deleting the element.

Study Elements for review

Application #: 21-372/ S-008 (b) (4) S-010

Drug Name: Aloxi (palonosetron hydrochloride) Intravenous Injection, 0.075 mg/1.5 mL

Previously Approved Indications:

- The prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy
- The prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

Proposed Indications:

- (S-008) Aloxi is indicated for the prevention of post operative nausea and vomiting (PONV) for up to three days after surgery.
- (b) (4)

Date Submitted: May 4, 2007

PDUFA DUE DATE: March 4, 2008

PREA Commitment from approval letter: N/A – approval letter has not been issued yet

Drug information:

- **Route of administration:** Intravenous injection
- **Formulation:** Injection
- **Dosage:**
- (b) (4)
- (b) (4)

Types of studies/ Study Design:

(b) (4) (1) the safety and tolerability of two does of IV palonosetron for the prevention of PNNV/ (b) (4), and (2) the efficacy of these two IV palonosetron doses to prevent PONV/ (b) (4)

Age group and population in which study will be performed:

The pediatric population is planned to consist of ASA status I, II, or III males and females ages (b) (4)

Number of patients to be studied or power of study to be achieved:

(b) (4)

Entry criteria:

(b) (4)

Exclusion criteria:

(b) (4)

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/s/

Iris Masucci
2/21/2008 09:56:52 AM
DDMAC REVIEWER

Laurie Burke
2/25/2008 11:54:28 AM
INTERDISCIPLINARY

MEMORANDUM OF TELECON

DATE: February 13, 2008, 1:00PM EST

APPLICATION NUMBER: NDA 21-372/S-008, (b) (4) S-010

BETWEEN:

Name: Craig Lehmann, Pharm.D., US Agent (August Consulting)
Dr. Dario Ceriani, Deputy Director, Regulatory Affairs, Helsinn
Dr. Mauro Capodiferro, Manager, Corporate Regulatory Affairs, Helsinn
Dr. Giuseppina Clerici, Manager Corporate Clinical Development, Helsinn

Phone: (304) 345-7563
Representing: Helsinn Healthcare SA

AND

Name: Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Nancy Snow, Medical Officer
Jagjit Grewal, RPM

Division of Gastroenterology Products, HFD-180

SUBJECT: Inform Sponsor of PeRC Committee Recommendations of Pediatric Plan

Helsinn Healthcare SA submitted their pediatric drug development plan dated November 2, 2007 in response to the FDA letter dated July 2, 2007. The sponsor's pediatric plan was reviewed earlier today by the Agency's PeRC Review Committee. This teleconference was to convey the PeRC committee's recommendations regarding the sponsor's pediatric plan.

1. The sponsor was informed that they should submit publications/data to justify their request for partial waiver in the 0 to 1 month of age population. The sponsor agreed to submit publications/data to support the requested waiver for 0 to 1 month of age.

2. The sponsor was also informed that they should incorporate a PK study in their pediatric plan to determine appropriate dosing. The sponsor indicated that the inclusion of a PK study with the pediatric plan was discussed in at the pre-sNDA meeting December 7, 2006 at which several FDA Pediatric Staff attended. During the pre-sNDA meeting, it was noted that for the very low I.V. palonosetron doses planned for the pediatric assessment study in pediatric patients (1 mcg/kg and 3 mcg/kg), the plasma levels are very low and largely below the limit of quantitation for the analytical method. Only the C_{max} and several hours of plasma concentrations after the C_{max} are expected to be captured in a PK analysis for the lowest dose (1 mcg/kg) and limited characterization for the 3 mcg/kg dose.

It was noted that at the pre-sNDA meeting, Dr. Lisa Mathis (PMHS) expressed concern that it would not be appropriate to stick children under these circumstances since useful PK data would not be obtained, and therefore it was suggested that the Sponsor perform modeling of the PK parameters for these low PONV (b) (4) doses instead of performing an in-vivo pediatric PK trial. The Sponsor agreed to perform the modeling instead of a pediatric PK study at the pre-sNDA meeting.

Dr. Gallo-Torres commented that he thinks this is a reasonable approach, that by itself the C_{max} is not expected to be useful without the additional PK parameters, and that the Sponsor should provide this explanation in a reply submission.

The sponsor expects to submit the requested information (justification of requested partial waiver and explanation of the basis for modeling of the PK parameters) within one week of today's teleconference.

Jagjit Grewal, MPH
Regulatory Project Manager

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/s/

Jagjit S Grewal
2/19/2008 02:24:50 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2008

Craig Lehmann **To:** US Agent for Helsinn Healthcare SA	Jagjit Grewal, MPH **From:** Regulatory Project Manager
Company: August Consulting	Division of Gastroenterology Products
Fax number: (512) 347-9375	**Fax number:** (301) 796-9905
Phone number: (512) 347-1755	**Phone number:** (301) 796-0846

Subject: NDA 21-372/S-008/S-010 (Aloxi I.V.) – Additional Labeling Comments

Total No. of pgs including cover: 3

DOCUMENT TO BE MAILED? NO

Dr. Lehmann,

Please find enclosed additional labeling comments in regards to NDA 21-372/S-008/S-010 for Aloxi (palonosetron hydrochloride) 0.075 mg/1.5 mL intravenous injection. I can be reached through the above contact information or email if you have any questions. Thank you.

Jagjit Grewal
Regulatory Project Manager
Division of Gastroenterology Products
Food & Drug Administration

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2120. Thank you.

Please refer to your April 27, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aloxi (palonosetron hydrochloride) 0.075 mg/1.5 mL intravenous injection.

We are reviewing the proposed labeling of your submission and have the following comments.

A. Container Label

1. Revise the established name and product strength so that is 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 is in accordance (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. Package Insert Labeling

1. HIGHLIGHTS OF PRESCRIBING INFORMATION
USE IN SPECIFIC POPULATIONS – referecnce "(8.4)" at the end of the sentence, "Safety and effectiveness in patients below the age of 18 years have not been established (8.4)"

2. HIGHLIGHTS OF PRESCRIBING INFORMATION
DOSAGE AND ADMINISTRATION – put a space between the words "administered" and "over" under the PONV subsection.

3. HIGHLIGHTS OF PRESCRIBING INFORMATION
"See 17 for PATIENT COUSELING INFORMATION and FDA-aproved patient labeling." The words "Patient" and "Labeling" should be capitalized.

4. FULL PRESCRIBING INFORMATION
Section 6 ADVERSE REACTIONS – delete the subsection heading (b) (4) Delete the space between the heading "ADVERSE REACTIONS" and the first paragraph beginning "Because clinical trials are conducted under widely varying conditions…"

5. FULL PRESCRIBING INFORMATION
Section 6.1 & 6.2 – the subheadings "CHEMOTHETAPY-INDUCED NAUSEA AND VOMITING" and "POSTOPERATIVE NAUSEA AND VOMITING" should not be written in all caps. The headings should be listed as "Chemotherapy-Induced Nausea and Vomiting" and "Postoperative Nausea and Vomiting." Do not underline these two subheadings.

6. FULL PRESCRIBING INFORMATION
Section 14.1 & 14.2 – the subheadings "CHEMOTHETAPY-INDUCED NAUSEA AND VOMITING" and "POSTOPERATIVE NAUSEA AND VOMITING" should not be written in all caps. The headings should be listed as "Chemotherapy-Induced Nausea and Vomiting" and "Postoperative Nausea and Vomiting." Do not underline these two subheadings.

7. FULL PRESCRIBING INFORMATION
Section 14.1 Chemotherapy-Induced Nausea and Vomiting – referring to the first paragraph after Table 5, correct the spelling of the word "the."

****
*** TX REPORT ***
****

TRANSMISSION OK

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RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2008

To: Craig Lehmann US Agent for Helsinn Healthcare SA	**From:** Jagjit Grewal, MPH Regulatory Project Manager
Company: August Consulting	Division of Gastroenterology Products
Fax number: (512) 347-9375	**Fax number:** (301) 796-9905
Phone number: (512) 347-1755	**Phone number:** (301) 796-0846

Subject: NDA 21-372/S-008/S-010 (Aloxi I.V.) – Additional Labeling Comments

Total No. of pgs including cover: 3

DOCUMENT TO BE MAILED? NO

Dr. Lehmann,

Please find enclosed additional labeling comments in regards to NDA 21-372/S-008/S-010 for Aloxi (palonosetron hydrochloride) 0.075 mg/1.5 mL intravenous injection. I can be reached through the above contact information or email if you have any questions. Thank you.

Jagjit Grewal
Regulatory Project Manager
Division of Gastroenterology Products
Food & Drug Administration

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/s/

Jagjit S Grewal
2/28/2008 11:06:20 AM
CSO

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, February 22, 2008 4:45 PM
To: 'Lehmann, Craig'
Cc: Grewal, Jagjit
Subject: NDA 21-372/S008/ (b) (4) S010 - FDA Revised Label 2/22/08
Attachments: Aloxi I.V. - FDA Revised Label 2.22.08.doc

Hello Craig,

Please find attached the Agency's revised label in response to the sponsor revised label dated 2/19/08. Additionally, I did received your email earlier today indicating the submission of a 4 month safety update, statement of good clinical practices, and revised AE Table 2 for labeling. Thank you.

Jagjit Grewal, MPH
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

8 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-372
5008/5010

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/s/

Jagjit S Grewal
2/27/2008 11:11:37 AM
CSO

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, February 14, 2008 5:45 PM
To: 'Lehmann, Craig'
Cc: Grewal, Jagjit
Subject: NDA 21-372/S008 (b) (4) S010 FDA Revised Labeling
Attachments: FDA Revised Label 2.14.08.doc

Hello Craig,

Please find attached the FDA's proposed changes to the labeling for NDA 21-372/S008 (b) (4) S010 Aloxi IV. Please review and feel free to contact me with any questions.

I will forward marked up carton and vial labeling once I received feedback from our reviewers. Thank you.

Jagjit Grewal, MPH
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

9 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-372
S008/S010

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/s/

Jagjit S Grewal
2/27/2008 11:05:46 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-372/S-008 (b) (4) 010

Helsinn Healthcare
Attn: Craig Lehmann
Authorized US Agent
c/o August Consulting , Inc
515 Capital of Texas Highway, Suite 150
Austin, Texas 78746

Dear Dr. Lehmann:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aloxi® (palonosetron) Injection, 0.025mg/5mL.

We also refer to your submission dated July 27, 2007 asking for additional clarification regarding the electronic data sets being requested in the July 2, 2007 filing letter.

We are reviewing the statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

The list below attempts to clarify our original requests as well as request additional information and data variables.

Part I. Response to specific questions in your July 27, 2007 submission

Response to Specific Question #1

For each of the two Studies (PALO-04-06 and PALO-04-07), please provide a single data set for the requested variables/information in a horizontal structure (i.e., one record per patient where each parameter for a given time interval becomes a single variable). This data set is further clarified. We are asking only for two analysis data sets, one per study, which we will analyze. It is not necessary for you to modify your original programs to reproduce hand-tabulated in-text tables. Please submit whatever SAS programs (source code listings) you have used to generate the tables or input for the tables.

Response to Specific Question #2

Please add to the two data sets (described in "Response to Specific Question#1") the additional time intervals (2 to 6 hours, 6 to 48 hours, and 6 to 72 hours) needed to generate the requested tables. (Part III of this correspondence shows the listing of variables to be included in the requested data sets.)

Response to Specific Question #3

For Study PALO-04-06, please provide your SAS programs which used the FAS population to generate Tables 12 to 21, and 23 while for Study PALO-04-07, please provide SAS programs which used the PFAS population to generate Tables 13, 14, 19, 20, 21, 22, 23, 24, 25, and 27.

In order to facilitate the review process, as requested in item #2 of FDA's filing letter dated July 2, 2007, for each of the two requested data, please add any additional variables that were needed to generate the requested tables.

As stated for #1, it is not necessary for you to modify your original programs so as to reproduce hand-tabulated in-text tables or to generate new tables from the new data sets. Please submit whatever SAS programs (source code listings) you have used to generate the tables or input for the tables.

Response to Specific Question #4

Please provide SAS programs to generate Table 21 for Study PALO-04-06 and Table 25 for Study PALO-04-07. You do not need to provide data for the severity of nausea.

Response to Specific Question #5

We are not requesting data for rescue medication nor the SAS programs used to analyze it.

Response to Specific Question #6

Please provide the SAS programs used to calculate the correlation between nausea and vomiting and the SAS analysis programs used for the Quality of Life assessments presented in Tables 3.12.1.1 to 3.12.1.6 in section 16.5 for Study PALO-04-06. The Quality of Life data are not being requested.

No data and no programs are being requested for Quality of Life for Study PALO-04-07.

Additional comments: If further clarification is still needed regarding this communication, we recommend you request a TCON.

Part II. Additional information request

1. [redacted] (b) (4)

2. Please add a new variable to the requested data set for Study PALO-04-07 as an indicator for potential un-blinding: "yes" for a patient involved in the un-blinding issue; or "no" for a patient not involved. (Part III of this correspondence shows the variable to be included in the requested data sets.)

3. Please add a new variable to the requested data set for Study PALO-04-07 as an indicator for an additionally enrolled patient: "yes" for additionally enrolled due to the un-blinding issue; "no" otherwise. (Part III of this correspondence shows the variable to be included in the requested data sets.)

4. Regarding your sensitivity analyses to support the validity of your primary efficacy analysis, we request you also compare the efficacy of the two treatment groups employing a non-parametric analysis of covariance as proposed by Gary Koch in: "Issues for Covariance Analysis of Dichotomous and Ordered Categorical Data from Randomized Clinical Trials and Non-parametric Strategies for Addressing Them" Statistics in Medicine, 17, 1863-1892 (1998).

Part III. List of variables to be included in the requested data set

The requested variables for each of the two data sets for Studies PALO-04-06 and PALO-04-07 are listed below:

Study identifier;
Investigator;
Patient discontinued prematurely;
Unique patient identifier;
Treatment name;
Full analysis set (yes or no);
Per-Protocol set (yes or no);
Modified full analysis set (yes or no);
Primary full analysis set (yes or no);
Gender;
Age;
Race;

Weight;
Smoking Status;
History of PONV and/or currently prone to motion sickness;
Type of surgery;
Complete Response assessed in the period of 0 to 24 hours (success or failure);
Complete Response assessed in the period of 24 to 72 hours (success or failure);
Complete Response assessed in the period of 0 to 2 hours (success or failure);
Complete Response assessed in the period of 0 to 6 hours (success or failure);
Complete Response assessed in the period of 6 to 24 hours (success or failure);
Complete Response assessed in the period of 24 to 48 hours (success or failure);
Complete Response assessed in the period of 0 to 48 hours (success or failure);
Complete Response assessed in the period of 0 to 72 hours (success or failure);
Complete Response assessed in the period of 2 to 6 hours (success or failure);
Complete Response assessed in the period of 6 to 48 hours (success or failure);
Complete Response assessed in the period of 6 to 72 hours (success or failure);
Complete Control assessed in the period of 0 to 24 hours (success or failure);
Complete Control assessed in the period of 24 to 72 hours (success or failure);
Complete Control assessed in the period of 0 to 2 hours (success or failure);
Complete Control assessed in the period of 0 to 6 hours (success or failure);
Complete Control assessed in the period of 6 to 24 hours (success or failure);
Complete Control assessed in the period of 24 to 48 hours (success or failure);
Complete Control assessed in the period of 0 to 48 hours (success or failure);
Complete Control assessed in the period of 0 to 72 hours (success or failure);
Complete Control assessed in the period of 2 to 6 hours (success or failure);
Complete Control assessed in the period of 6 to 48 hours (success or failure);
Complete Control assessed in the period of 6 to 72 hours (success or failure);
Emesis assessed in the period of 0 to 24 hours (success or failure);
Emesis assessed in the period of 24 to 72 hours (success or failure);
Emesis assessed in the period of 0 to 2 hours (success or failure);
Emesis assessed in the period of 0 to 6 hours (success or failure);
Emesis assessed in the period of 6 to 24 hours (success or failure);
Emesis assessed in the period of 24 to 48 hours (success or failure);
Emesis assessed in the period of 0 to 48 hours (success or failure);
Emesis assessed in the period of 0 to 72 hours (success or failure);
Emesis assessed in the period of 2 to 6 hours (success or failure);
Emesis assessed in the period of 6 to 48 hours (success or failure);
Emesis assessed in the period of 6 to 72 hours (success or failure);
Time to treatment failure;
Indicator for potential un-blinding issue for Study PALO-04-07 (yes for patient involved, no for patient not involved);
Indicator for additional enrolled patients due to un-blinding issue for Study PALO-04-07 (yes for patient additionally enrolled, no otherwise);

If you have questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, M.B.A, RPh
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
10/9/2007 08:35:32 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Devi Kozeli **Project Specialist** **Division of Cardiovascular and Renal Products (DCRP)** **WO Bldg #22**	**Division of Gastroenterology Products** **Giuseppe Randazzo** **Project Manager** **301- 796-0980**

DATE :	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 28, 2007		21-372/SE1 – 008 (QS) 21-372/SE8 – 010 (QS)	IR response	June 21, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aloxi (palonosetron)	High	Antiemetic	August 24, 2007 **If possible, a mid August completion date is preferred.**

NAME OF FIRM: Helsinn Healthcare SA

REASON FOR REQUEST

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

COMMENTS/BACKGROUND/SPECIAL INSTRUCTIONS:

(b) (4)

Please review the through QT study PALO-03-11.

If you have any questions or concerns please let me know. The submission is a hybrid (electronic and paper); if there is something you need and can not find, please let me know and I will contact the sponsor.

Thanks

Giuseppe (6-0980)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Giuseppe Randazzo	☒ EMAIL ☒ DFS ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Giuseppe Randazzo
7/10/2007 03:33:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **New Drug Microbiology Staff** **Jim McVey (6-1572)** **Microbiologist Team Leader** **WO Bldg #21, Room 3652**	FROM: **Division of Gastroenterology Products** **Giuseppe Randazzo (6-0980)** **Project Manager**

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT
June 20, 2007	N/A	**21-372/SE1-008** (b) (4) **21-372/SE8-010**	**Efficacy Supplement (s)**	**April 27, 2007**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aloxi™ (palonosetron hydrochloride)	**Low**	**Antiemetic**	**January 4, 2008** **PDUFA date: March 4, 2008**

NAME OF FIRM: **Helsinn Healthcare**

REASON FOR REQUEST

I. GENERAL

OTHER (SPECIFY BELOW):
☑ OTHER: Micro Review

COMMENTS/SPECIAL INSTRUCTIONS:

Aloxi™ (palonosetron hydrochloride) was approved on 7/25/2003 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.

On May 4, 2007 we received efficacy supplement 008 with the proposed indication of ***the prevention of postoperative*** (b) (4) ***nausea and vomiting (PONV)*** (b) (4) ***for up to*** (b) (4)

We unbundled this submission into (b) (4)010.

21-372/SE1-008 : new indication: PONV
(b) (4)

21-372/SE8-010 : removal of QT safety information currently found in FPI

Please see EDR under letter date: 27-APR-2007; doc type SE1; seq no 008

This submission is a hybrid. If the information you need to review is unavailable in the EDR please let me know and I will acquire the Micro paper volumes.

Please review these applications from a Micro perspective.

Thank you for your time and consideration.
Giuseppe Randazzo

SIGNATURE OF REQUESTER G.R.	METHOD OF DELIVERY (Check one) ☑ DFS ☑ EMAIL ☐ MAIL ☐ HAND
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/s/

Giuseppe Randazzo
6/20/2007 01:59:26 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Div. Of Drug Marketing, Advertising and Communication** **Michael Brony (301-796-0576)** **Consumer Safety Officer** **Center of Drug Evaluation and Research (CDER)**	FROM: **Division of Gastroenterology Products** **Giuseppe Randazzo (301- 796-0980)** **Project Manager**

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENT
June 18, 2007	N/A	**21-372/SE1-008** (b) (4) **21-372/SE8-010**	**Efficacy Supplement (s)**	**April 27, 2007**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aloxi™ (palonosetron hydrochloride)	**Low**	**Antiemetic**	**January 4, 2008**

NAME OF FIRM: **Helsinn Healthcare**

REASION FOR REQUEST

I. GENERAL

OTHER (SPECIFY BELOW):
☑ OTHER: Label Review

COMMENTS/SPECIAL INSTRUCTIONS:

Aloxi™ (palonosetron hydrochloride) was approved on 7/25/2003 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.

With the following caveat:
DOSAGE AND ADMINISTRATION
Dosage for Adults
The recommended dosage of Aloxi is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of Aloxi™ within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

On April 27, 2007 we received efficacy supplement 008 with the proposed indication of *the prevention of postoperative* (b) (4) *nausea and vomiting (PONV* (b) (4) *for up* (b) (4)

We unbundled this submission into (b) (4) 010.

21-372/SE1-008 : new indication: PONV
(b) (4)

21-372/SE8-010 : removal of QT safety information currently found in FPI

The labeling content can be found in the EDR under letter date: 27-APR-2007; doc type SE1; seq no 008

It would be greatly appreciated if you could review this label.

Thank you for your time and consideration.
Giuseppe Randazzo

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
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/s/

Giuseppe Randazzo
6/19/2007 04:25:04 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **Office of Surveillance and Epidemiology (OSE)** **Tanya Clayton (301-796-0871)** **Regulatory Project Manager** **Center of Drug Evaluation and Research (CDER)**	FROM: **Division of Gastroenterology Products** **Giuseppe Randazzo (301- 796-0980)** **Project Manager**

DATE: **June 18, 2007**	IND NO. N/A	NDA NO. **21-372/SE1-008** (b) (4) **21-372/SE8-010**	TYPE OF DOCUMENT: **Efficacy Supplement (s)**	DATE OF DOCUMENT **April 27, 2007**

NAME OF DRUG **Aloxi™ (palonosetron hydrochloride)**	PRIORITY CONSIDERATION **Low**	CLASSIFICATION OF DRUG **Antiemetic**	DESIRED COMPLETION DATE **January 4, 2008**

NAME OF FIRM: **Helsinn Healthcare**

REASION FOR REQUEST

I. GENERAL

OTHER (SPECIFY BELOW):
☑ OTHER: Trade name review

COMMENTS/SPECIAL INSTRUCTIONS:

Aloxi™ (palonosetron hydrochloride) was approved on 7/25/2003 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.

With the following caveat:
DOSAGE AND ADMINISTRATION
Dosage for Adults
The recommended dosage of Aloxi is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of Aloxi™ within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

On April 27, 2007 we received efficacy supplement 008 with the proposed indication **of** ***the prevention of postoperative*** (b) (4) ***nausea and vomiting (PONV*** (b) (4) ***for up to*** (b) (4)

We unbundled this submission into (b) (4) 010.

21-372/SE1-008 : new indication: PONV
(b) (4)

21-372/SE8-010 : removal of QT safety information currently found in FPI

The labeling content can be found in the EDR under letter date: 27-APR-2007; doc type SE1; seq no 008

Please review the trade name.

Thank you for your time and consideration.
Giuseppe Randazzo

SIGNATURE OF REQUESTER G.R.	METHOD OF DELIVERY (Check one) ☑ DFS ☑ EMAIL ☐ MAIL ☐ HAND
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/s/

Giuseppe Randazzo
6/20/2007 12:37:43 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-372 Supplement # 008 (b) (4)/010 Efficacy Supplement Type SE-1 (008) (b) (4) SE-8 (010)

Proprietary Name: Aloxi
Established Name: Palonosetron Hydrochloride
Strengths: 0.075 mg/1.5 mL Intravenous Injection

Applicant: Helsinn Healthcare SA
Agent for Applicant (if applicable): Craig Lehmann, Pharm.D. (US Agent-August Consulting)

Date of Application: April 27, 2007
Date of Receipt: May 4, 2007
Date clock started after UN: N/A
Date of Filing Meeting: June 14, 2007
Filing Date: July 03, 2007
Action Goal Date (optional): February 29, 2008 User Fee Goal Date: **March 4, 2008**

Indication(s) requested:

S-008: The prevention of postoperative nausea and vomiting (PONV) for up to (b) (4) (b) (4) (b) (4)

S-010: Removal of QT safety information currently found in the label.

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the*

User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NCE Exclusivity Expires on July 25, 2008

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☒
     This application is: All electronic ☐ Combined paper + eNDA ☒
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☒

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

- Proposed Labeling
- Application Summary, Section 3
- Study PALO-03-05 PK datasets
- Study PALO-03-10 PK datasets
- Phase 3 Study PALO-04-06 datasets
- Phase 3 Study PALO-04-07 datasets
- Thorough QT/QTc Study PALO-03-11 datasets
- ISS datasets
- Case Report Tabulations, Section 11

Additional comments:

3. This application is an eCTD NDA. YES ☐
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
Pediatric Waiver (0 to 1 month of age) YES ☒ NO ☐
Pediatric Deferral (1 month to 16 years of age) – see volume 44 of 332

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☐ NO ☒
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
  Doc room staff had 04-MAY-2007 a request to change to 04-MAR-2008 was emailed.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **No INDs were referenced on Form 356h; however NDA 21-372 Original Submission and** (b) (4) **were referenced. (IND 39,797)**

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) May 3, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Pre-sNDA Meet: December 7, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) December 17, 2004; March 7, 2005; March 8, 2005; March 9, 2005 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 14, 2007

NDA #: 21-372/S-008/(b) (4)/S-010

DRUG NAMES: Aloxi™ (Palonosetron Hydrochloride) Injection, 0.075 mg/1.5 mL

APPLICANT: Helsinn Healthcare SA
Agent for Applicant (if applicable): Craig Lehmann, Pharm.D. (US Agent-August Consulting)

BACKGROUND:

NDA 21-372, approved 7/25/2003 for 1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic chemotherapy, and 2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

NDA 21-372/S-008/(b) (4)/S-010 Aloxi (palonosetron hydrochloride) proposes to make the following changes to their current label.

1. S-008: Add an indication for the prevention of postoperative nausea and vomiting (PONV) for up to (b) (4)

2. (b) (4)

3. S-010: Remove QT information in the Warnings and Precautions section

4. Add data throughout the label encompassing numbers 1, 2, and 3 above.

Aloxi is approved in 52 other countries for CINV, but to the best of my knowledge, this is the first application proposing PONV (b) (4)

ATTENDEES:

Korvick, Joyce A
Gallo Torres, Hugo E
Snow, Nancy
Lu, Yong De
Lee, Sue Chih H
Bashaw, Edward D
Ahn, Hae Young
Chen, Wen Jen
Lewis, David B
Patel, Hasmukh B
Delasko, Jeanne
Welch, Mike
CDER-ONDIO-SEALD
Malek, Khairy W
Clayton, Tanya
Corken, Ann
Green, Lanh
Furness, Melissa
CDER SEALD Labeling
Anderson, Robin
Burke, Laurie B
Trentacosti, Ann Marie
Kennedy, Dianne L

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Hugo Gallo-Torres
Secondary Medical:	Nancy Snow
Statistical:	Wen-Jen Chen
Pharmacology:	Sushanta Chakder
Statistical Pharmacology:	N/A
Chemistry:	Yong De Lu
Environmental Assessment (if needed):	
Biopharmaceutical:	Sue Chih Lee
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	

OPS: N/A
Regulatory Project Management: Giuseppe Randazzo
Other Consults:

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Giuseppe Randazzo/ Jagjit Grewal (10/15/07)
Regulatory Project Manager

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

/s/

Jagjit S Grewal
2/29/2008 06:51:24 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-372/S-008 (b) (4) 010

Helsinn Healthcare
Attn: Craig Lehmann
Authorized US Agent
c/o August Consulting , Inc
515 Capital of Texas Highway, Suite 150
Austin, Texas 78746

Dear Dr. Lehmann:

Please refer to your April 27, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aloxi® (palonosetron) Injection, 0.07525 mg/1.5mL.

We also refer to our June 11, 2007 meeting to discuss the unbundling of this submission.

We acknowledge your acceptance of the unbundling and the necessity of administratively splitting S-008 into 3 submissions.

Therefore your April 27, 2007 submission has been administratively split into the following:

S-008: for post operative nausea and vomiting (PONV)
(b) (4)
S-010: for the removal of QT safety information currently found in the label

The following information applies to the applications listed above:

- Name of Drug Product: Aloxi® (palonosetron hydrochloride) Injection, 0.075 mg/1.5mL
- NDA Number: 21-372
- Supplement numbers: 008, (b) (4) 010
- Review Priority Classification: Standard (S)
- Date of supplement: April 27, 2007
- Date of receipt: May 4, 2007

These supplemental applications propose to add the following indication to the current FDA approved Aloxi® labeling: The prevention of postoperative (b) (4) nausea and vomiting (PONV/ (b) (4) for up (b) (4) Additionally, you propose to remove QT safety data from your current label.

We have completed our filing reviews and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on July 3, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

I. Biostatistics

1. Please provide the following information for Studies PALO-04-06 and PALO-04-07. Please provide the data in electronic format consistent with **http://www.fda.gov/cder/regulatory/ersr/ectd/htm** to include the following variables:

   - Study identifier;
   - Investigator;
   - Patient discontinued prematurely;
   - Unique patient identifier;
   - Treatment name;
   - Full analysis set;
   - Per-Protocol set;
   - Modified full analysis set;
   - Primary full analysis set;
   - Gender;
   - Age;
   - Race;
   - Weight;
   - Smoking Status;
   - History of PONV and/or currently prone to motion sickness;
   - Complete Response assessed in the period of 0 to 24 hours (success or failure);
   - Complete Response assessed in the period of 24 to 72 hours (success or failure);
   - Complete Response assessed in the period of 0 to 2 hours (success or failure);
   - Complete Response assessed in the period of 0 to 6 hours (success or failure);
   - Complete Response assessed in the period of 6 to 24 hours (success or failure);
   - Complete Response assessed in the period of 24 to 48 hours (success or failure);
   - Complete Response assessed in the period of 0 to 48 hours (success or failure);
   - Complete Response assessed in the period of 0 to 72 hours (success or failure);
   - Complete Control assessed in the period of 0 to 24 hours (success or failure);
   - Complete Control assessed in the period of 24 to 72 hours (success or failure);
   - Complete Control assessed in the period of 0 to 2 hours (success or failure);
   - Complete Control assessed in the period of 0 to 6 hours (success or failure);
   - Complete Control assessed in the period of 6 to 24 hours (success or failure);

- Complete Control assessed in the period of 24 to 48 hours (success or failure);
- Complete Control assessed in the period of 0 to 48 hours (success or failure);
- Complete Control assessed in the period of 0 to 72 hours (success or failure);
- Severity of Nausea assessed in the period of 0 to 24 hours (success or failure);
- Severity of Nausea e assessed in the period of 24 to 72 hours (success or failure);
- Severity of Nausea assessed in the period of 0 to 2 hours (success or failure);
- Severity of Nausea assessed in the period of 0 to 6 hours (success or failure);
- Severity of Nausea assessed in the period of 6 to 24 hours (success or failure);
- Severity of Nausea assessed in the period of 24 to 48 hours (success or failure);
- Severity of Nausea assessed in the period of 0 to 48 hours (success or failure);
- Severity of Nausea assessed in the period of 0 to 72 hours (success or failure);
- Emesis assessed in the period of 0 to 24 hours (success or failure);
- Emesis assessed in the period of 24 to 72 hours (success or failure);
- Emesis assessed in the period of 0 to 2 hours (success or failure);
- Emesis assessed in the period of 0 to 6 hours (success or failure);
- Emesis assessed in the period of 6 to 24 hours (success or failure);
- Emesis assessed in the period of 24 to 48 hours (success or failure);
- Emesis assessed in the period of 0 to 48 hours (success or failure);
- Emesis assessed in the period of 0 to 72 hours (success or failure);
- Impact of PONV on daily life (yes or no);
- Time to first emetic episode;
- Time to treatment failure;

We understand that some variables listed above may have been provided in earlier electronic submissions, however to facilitate the review process, please provide them again per this request.

2. For Study PALO-04-06, please submit the statistical efficacy analysis (SAS) programs used to generate tables for Table 12 to Table 23 (total of 12 tables) and results regarding Quality of Life, presented in Section 11 "Efficacy Evaluation" of Volume 216.

   Similarly, for Study PALO-04-07, please submit the statistical efficacy analysis programs used to generate tables from Table 13 to Table 36 (total of 24 tables), presented in section 11 "Efficacy Evaluation" of Volume 255.

   Regarding the data set described in 1 (above), please add any additional variables needed (variables we may have not included in the above list) for the analyses programs requested in 2. Please modify the programs to be able to input data from the data set described in 1.

3. Regarding the treatment allocation procedure described in the section of 9.8.1.5.1 "Primary Efficacy analyses" for both studies (PALO-04-06 and PALO-04-07), please provide the following supportive information:

    i. The algorithm and simulation program used to generate the re-randomization list and p-values.
    ii. Articles and/or other justification to support the use of this re-randomization technique.

4. Please provide the detailed algorithm (proposed by R.G. Newcombe and D.G. Altman in "Statistics with Confidence") used to calculate the 95% CI for proportions and for the difference between two proportions described in the section of 9.8.1.1 "Generational Considerations" for both studies.

We are providing the above comments to give you preliminary notice of potential review issues. At this time, we have not identified any filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until December 13, 2008. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

If you have any questions, call Giuseppe Randazzo, Project Manager, at (301) 796-0980.

Sincerely,

{See appended electronic signature page}

Brian Strongin, M.B.A, RPh
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
7/2/2007 03:14:53 PM