Attachment One

PALO-99-03

Clinical & Statistical Study Report: Volume 1.117, page 1

Synopsis: Volume 1.117, page 4

Protocol: Volume 1.118, page 5

List of Investigators: Volume 1.119, page 1

Related Publications: Volume 1.120, page 138

Palo-99-04

Clinical & Statistical Study Report: Volume 1.135, page 1

Synopsis: Volume 1.135, page 4

Protocol: Volume 1.136, page 4

List of Investigators: Volume 1.136, page 257

Related Publications: Volume 1.137, page 404

Palo-99-05

Clinical & Statistical Study Report: Volume 1.156, page 1

Synopsis: Volume 1.156, page 4

Protocol: Volume 1.157, page 5

List of Investigators: Volume 1.158, page 1

Related Publications: Volume 1.160, page 146

cc:
Draft: BKS/November 1, 2002
Final: BKS/November 1, 2002
Filename: reviews/Palonosetron Admin Review.doc

ADMINISTRATIVE REVIEW

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/s/

Brian Strongin
11/1/02 03:52:38 PM
CSO

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*** TX REPORT ***
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 25, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Approval Letter for NDA 21-372. Enjoy!

Total no. of pages including cover: 16

Comments:

Document to be mailed: ☐ YES ☑ NO

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/s/

Julie Beitz
7/25/03 08:45:03 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 11, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473
Subject: FDA Mark-Up of Your Proposed Package Insert Submitted September, 2002 for NDA 21-372; Palonosetron	
Total no. of pages including cover: 3	

Comments:

A clean copy of our mark-up of your proposed package insert submitted September 25, 2002 is attached. I have also e-mailed this labeling. When you send your response, please mark-up the clean copy so that your changes are clearly indicated. Please note that we are talking with the Office of Medical Policy about including the comparator names because of the potential for comparative claims and may have additional changes. Please refer to section III.A.4 in the draft Guidance for Industry on the Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format. Thanks.

Document to be mailed: ☐ YES ☑ NO

16 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Brian Strongin
7/11/03 10:28:30 AM
CSO

Lehmann, Craig

From: Lehmann, Craig
Sent: Tuesday, July 22, 2003 8:40 AM
To: Brian Strongin (E-mail)
Subject: NDA 21-372, Sponsor-proposed revised labeling dated July 22, 2003, in follow-up to FDA teleconference held July 21, 2003

Dear Mr. Strongin:

In follow-up to the FDA labeling teleconference held yesterday, please find attached the subject Sponsor-proposed revised labeling as we discussed. Proposed revisions are highlighted in yellow.

Please let me know if you wish further information.

I will call you shortly.

Best Regards,
Craig

NDA 21-372 Sponsor Proposed Le...

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CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: January 9, 2003	DUE DATE: February 18, 2003	ODS CONSULT #: 02-0068-2

TO: Robert Justice, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Brian Strongin
Project Manager, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME:	**IND SPONSOR:** Helsinn Healthcare SA
[redacted] (Palonosetron Hydrochloride Injection) 0.25 mg (0.05 mg/mL) **IND #:** [redacted]	

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the additional information submitted by the sponsor regarding the proposed proprietary name [redacted]. DMETS previously did not recommend the use of the name [redacted] (See ODS Consult # 02-0068)

RECOMMENDATIONS: DMETS does not recommend the use of the proprietary name [redacted]. The studies, in addition to the information on additional discriminating features and context of use submitted by the sponsor, have not provided a persuasive argument to diminish our concerns with potential confusion between [redacted] and [redacted]. **However, after review of additional information submitted by the sponsor and the fact that the firm will not market this product with the 0.75 mg strength, DMETS has no objections to use of the proprietary name, Aloxi.** In addition, DMETS recommends implementation of the labeling revision outlined in section IV of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. Parklawn Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 25, 2003

IND#

NAME OF DRUG:
(Palonosetron Hydrochloride Injection)
0.25 mg (0.05 mg/mL)

IND HOLDER: Helsinn Healthcare SA

I. INTRODUCTION:

This consult is in response to a December 26, 2002, submission from August Consulting, an Authorized Representative for the IND, requesting reconsideration of the proprietary name, Reference is made to ODS Consult # 02-0068, dated May 7, 2002, in which the Division of Medication Errors and Technical Support (DMETS) found the name objectionable due to the sound-alike potential with The sponsor has currently submitted additional information, including an independent analysis conducted by the to support approval of the proprietary name, Container labels and carton labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor initially proposed two proprietary names in addition to Aloxi and and Aloxi were reviewed on May 7, 2002 (ODS Consult #02-0068) and found unacceptable from a safety perspective as was which was reviewed on August 22, 2002 (ODS Consult #02-0068-1).

In a correspondence dated April 5, 2002, the sponsor explained that one product strength, either 0.25 mg or 0.75 mg will be selected for the NDA and marketing based on phase 3 efficacy data. The project manager was contacted on March 12, 2003, and informed DMETS that the firm will market the 0.25mg strength.

PRODUCT INFORMATION

is the proposed proprietary name for Palonosetron Hydrochloride Injection. Palonosetron's proposed indication is for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherpy, including highly emetogenic chemotherapy. The recommended dosage is 0.25 mg once daily in a single intravenous dose. This product is intended to be administered once per chemotherapy cycle, approximately every 2-5 weeks depending on the chemotherapy regimen. will be supplied as 0.05 mg/mL in a 5 mL vial.

II. RISK ASSESSMENT

A. ———

The — conducted two studies to evaluate the potential for error between and currently marketed brand/generic drug products. The — concentrated evaluation methods in four areas. In Section A, 100 physicians evaluated for sound-alike/look-alike similarity, medical term similarity, and hyperbole issues. Section B involved 100 participating pharmacists in interpretation studies of verbal and handwritten prescriptions for potential name confusion. In Section C, a computerized analysis of phonologic and orthographic similarities between and existing drug names was conducted. In Section D, a Nomenclature Advisory Board reviewed the safety data for

1. Section A ———

— asked 100 participating physicians to view the test name, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if there were any medical terms that could be similar to the test name. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from 100 participating physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following prescription.

IV push – over 30 seconds, 30 minutes prior to chemotherapy

— identified the names *Celebrex, Centrax, Sinemet,* and as having sound-alike similarity and *Avonex, Celebrex, Centrax,* and as having look-alike similarity. The medical term *Cervix* was thought to have similarities with Also, 1% of physicians responding thought that the name was suggestive of an antibiotic.

DMETS Response:

Although — indicates that 270 physicians were asked to participate in this phase of the study, the response rate was only 37% (100 physicians). — notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predictive value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed. Additionally, DMETS notes that this study asked physicians, instead of pharmacists, to identify any sound-alike or look-alike products. Physicians do not usually interpret prescriptions and thus the section would have been more effective if pharmacists had been included. This issue is also dependent upon the specialty of the physician. However, — did not provide any medical specialty information on the respondents.

DMETS considered the potential for name confusion between and Sinemet in the review dated May 7, 2002, and decided that the risk of dispensing the wrong medication should be low based on lack of convincing sound-alike similarities and differences

between the medications. DMETS continues to have concerns with the sound-alike properties between [redacted] and [redacted]. Of other names identified by physicians in the — study as having sound-alike or look-alike similarity with [redacted] DMETS believes the risk of confusion is minimal given the differences between the drug characteristics and lack of convincing look-alike and sound-alike potential. The term "cervix" should not present confusion for the name [redacted] since the context for use would lessen the potential for errors.

Section B – Handwritten and Verbal Analysis: Pharmacists

— provided one hundred pharmacists (50 retail and 50 hospital) with a verbal and written prescription (see above sample) for [redacted] The objective of this phase is to determine if any of the sample [redacted] prescriptions would be interpreted as a currently marketed brand or established name product. All of the respondents correctly identified the name [redacted] from verbal and handwritten prescriptions.

DMETS Response:

As noted with the physician response rate, — indicates that the response rate in this portion of the study was 39% (100 pharmacists). Again, there are limitations in the predictive value of these studies, primarily due to the sample size. Written and verbal prescriptions were collected from the physicians. Therefore, each of the one hundred pharmacists would have received a verbal and handwritten prescription to review. This methodology introduces bias because the participating pharmacists would have exposure to the drug name before evaluation of the second sample.

The inclusion of "chemo" in the signatura (*IV push over 30 sec., 30 min. prior to chemo.)* for these prescriptions presented contains a link to the indication of use for the proposed product and provides a clue to the reader that this product may have something to do with chemotherapy. Additionally, it is highly unlikely that pharmacists would misinterpret a prescription as [redacted] when the sample contained the detailed directions in the aforementioned signatura. A more challenging test of confusion would have been a prescription that ordered [redacted] "as directed", without reference to indication or route of administration.

In the verbal prescription conducted by DMETS [redacted] was ordered as follows:

[redacted] *0.25 mg*
One
Use as directed.

One study participant misunderstood the verbal order for [redacted] to be [redacted] In the above example provided by DMETS, a pharmacist who inadvertently misinterpreted [redacted] as [redacted] would most likely question the order since [redacted] not associated with a "mg" dosing amount. However, postmarketing experience has also shown errors occurring with products having look-alike and/or sound-alike names regardless of other differentiating factors. Therefore, DMETS has concerns with the sound-alike potential between [redacted] and [redacted]

Section C – Computer-Assisted Analysis

conducted a "comprehensive search of medical references" to identify brand and established names that may sound-alike or look-alike to the proposed name. Fourteen names were identified. — analyzed the names using their " database and using a "Phonological and Orthographical Similarity Analysis." The "Phonological and Orthographical Similarity Analysis" identifies a threshold of similarity between and the fourteen products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product.' identified 14 proprietary names as having look-alike and/or sound-alike potential with the proposed name . — concludes that the results "...show infrequent overlap in product profiles among purportedly similar drug names..." and that, " will be distinguished from other products, including , in real-world practice."

DMETS Response:

With the exception of DMETS does not have concerns with the proprietary names identified by — the Analysis, due to lack of convincing look-alike or sound-alike similarities and the presence of differentiating features. Although and have some distinguishing features, both are injectable drug products intended for single dose for a specified period of time. DMETS has the following comments concerning the methodology employed by — to determine phonologic and orthographic similarity between name pairs:

- The phonologic and orthographic devices yield results which in some cases have no resemblance to the study name. Examples from this study are "Vanocin" and "Vexol", which bear little resemblance to
- The order of syllables must not play a factor in the phonologic similarity rating or the bigram measure. For example, although "vex" in comes as the second syllable, it is the first syllable in Vexol. Vexol had the highest rating in the bigram measure even though it sounds little like

Section D - Pharmacists' Analysis –

Ten actively practicing retail and hospital pharmacists provided an independent analysis of the proposed proprietary name, by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study and determined that based on their experience the risk of name confusion between and is minimal. The review board's analysis was favorable for Key differentiating features between and were summarized in an Executive Summary.

DMETS Response:

The has submitted information to support the proposed proprietary name, also specifically details the safety profile between the names and

DMETS acknowledges comments regarding differences in the distribution of — and . — states that — is most frequently purchased by the Orthopedist from the wholesaler and administered by intra-articular injection in the office. DMETS agrees that under these conditions, it would be unlikely for an error involving confusion between — and to occur. However, it is possible that an orthopedic outpatient clinic located in a hospital could order — from the hospital pharmacy. Such a verbal order might easily be misunderstood as Although DMETS' primary concern is confusion of and in the hospital setting, it is important to note that — is available through internet sources such as Destination Rx and Drugstore.com and may be ordered through retail pharmacies as well. DMETS agrees with the J — that one possible distribution route is that the patient purchases — and brings it to the physician for intra-articular injection. This scenario presents one additional opportunity for confusion between — and

If a prescription for — is inadvertently misinterpreted as the pharmacist may not question the strength since — is available without a strength and will be available in only one strength (0.25 mg/5 mL). Conversely, a prescription for may be ordered without a strength since only one strength of will be available in the marketplace.

DMETS also acknowledges differences in physician prescribing population, practice setting, and patient populations for these two products. However, postmarketing experience has also shown errors occurring with products having look-alike and/or sound-alike names regardless of other differentiating factors.

In summary, although — is mainly distributed directly to physicians, there is some potential that — will be kept on hospital pharmacy shelves. Confusion for this name pair may occur during initial marketing when product recognition is low. DMETS has concerns regarding the safety of concurrent marketing of and — because of the positive response in the DMETS prescription study, the strong sound-alike properties of these products, and that both and — are injectable drug products intended for single dose administration for a specified period of time.

III. RISK ASSESSMENT - ALOXI:

In a review dated May 7, 2002 (ODS Consult #02-0068), DMETS found the name Aloxi unacceptable. In part, that decision was made because of the shared numerals in the strengths of those products, Aloxi 0.75 mg and Alora 0.075 mg. It has come to the attention of DMETS that Aloxi will *not* be marketed with the 0.75 mg strength. Because of other differences between the products including route of administration and dosage form (transdermal patch vs. parenteral product for intravenous use), and the differences in physician prescribing population, practice setting, and patient populations for these two products, DMETS has reconsidered the safety profile of Aloxi and does not object to the use of the proprietary name in the marketplace.

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels and carton labeling of [redacted] DMETS has focused on safety issues relating to possible medication errors and has identified one area of possible improvement, which might minimize potential user error.

GENERAL COMMENT

Revise the strength on container labels and carton labeling as follows:

0.25 mg/5 mL
(0.05 mg/mL)

V. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name [redacted] The studies, in addition to the information on additional discriminating features and context of use submitted by the sponsor, have not provided a persuasive argument to diminish our concerns with potential confusion between [redacted] and [redacted]

B. After review of additional information submitted by the sponsor and the fact that the firm will not market this product with the 0.75 mg strength, DMETS has no objections to use of the proprietary name, Aloxi.

C. DMETS recommends implementation of the labeling revision outlined in section IV of this review to minimize potential errors with the use of this product.

Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Charles Hoppes
3/18/03 01:38:55 PM
PHARMACIST

Alina Mahmud
3/18/03 01:50:39 PM
PHARMACIST

Jerry Phillips
3/18/03 02:00:08 PM
DIRECTOR

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 16, 2002	**DUE DATE:** Sept. 17, 2002	**ODS CONSULT #:** 02-0068-1

TO: Robert Justice, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Brian Strongin
Project Manager
HFD-180

PRODUCT NAME: [redacted] (Palonosetron Hydrochloride Injection) 0.25 mg (0.05 mg/mL) and **IND #:** [redacted]	**IND SPONSOR:** Helsinn Healthcare SA

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products, HFD-180, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary name [redacted]

The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names or established names from the signature date of this document forward.

/S/ /S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 22, 2002

IND# [redacted]

NAME OF DRUG: [redacted]
(Palonosetron Hydrochloride Injection)
0.25 mg (0.05 mg/mL)

IND HOLDER: Helsinn Healthcare SA

I. INTRODUCTION:

This consult is written in response to a request from the Division of Division of Gastrointestinal and Coadgulation Drug Products for an assessment of the proposed proprietary name, [redacted] Draft container labels and carton labeling were not submitted with this consult since this application is in the IND phase.

PRODUCT INFORMATION

[redacted] is the proposed proprietary name for Palonosetron Hydrochloride Injection. Palonosetron hydrochloride is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy. The recommended dose is 0.25 mg [redacted] as a single intravenous dose administered as a 30 second bolus 30 minutes prior to emetogenic chemotherapy. [redacted] will be administered once per chemotherapy cycle, approximately every 2 to 5 weeks, depending on the chemotherapy regimen.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to a degree where potential confusion between drug names could occur under the usual

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in table 1 (see below), along with the usual dosage and available dosage forms.

2. DDMAC did not have concerns about the name [redacted] with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
[redacted]	**Palonosetron HCL Injection 0.25 mg (0.05 mg/mL) or**	**0.25 mg [redacted] in a single dose, intravenously each chemotherapy cycle, approximately every 2- 5 weeks.**	
Oracit	Oral Citrate Solution 490 mg sodium citrate and 640 mg citric acid per 5 mL.	10 to 30 mL diluted with water, after meals and before bedtime.	**LA/SA
Omnicef	Cefdinir Capsules 300 mg Oral Suspension 125 mg/5 mL	600 mg per day for 10 days, either as once-daily or twice-daily dosing.	**SA
Ansaid	Flurbiprofen Tablets 50 mg and 100 mg	200 to 300 mg per day in 2-4 divided doses.	**SA
Emcyt	Estramustine Phosphate Sodium equivalent 140 mg estramustine phosphate (12.5 mg sodium/capsule)	14 mg/kg/day in 3 or 4 divided doses (dosage range 10 to 16 mg/kg/day).	**SA

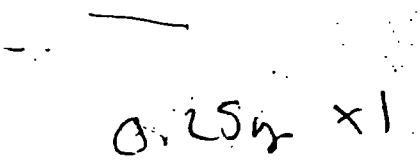
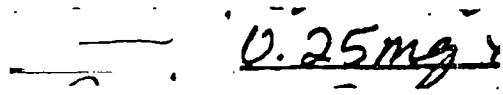
*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name.

These studies employed a total of 16 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for [redacted] (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

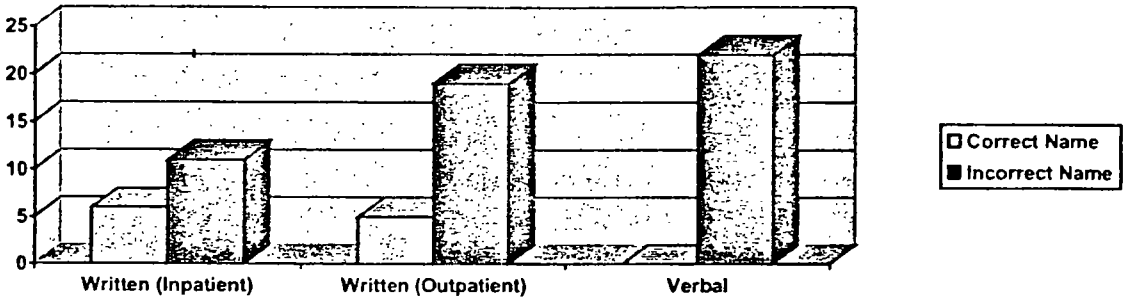
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	[redacted] 0.25 mg, take 1 time today at 1pm before clinic.
Inpatient RX: 	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	32	17 (53%)	6 (35%)	11 (65%)
Written Outpatient	39	24 (62%)	5 (21%)	19 (79%)
Verbal	35	22 (63%)	0 (0%)	22 (100%)
Total	106	63 (59%)	11 (17%)	52 (83%)



Among the verbal prescription study participants for [redacted] 22 of 22 (100%) of the participants interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of [redacted] The incorrect responses were *Onacet (8), Anacet (3), Alacet (2), Alasert (1), Amacet (1), Anafette (1), Anasept (1), Onocet (1), Oniset (1), Onofect (1), Onosette (1), and Ulcet (1).*

Among the written prescription study participants for [redacted] 30 of 41(73%) participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted]. The incorrect responses were *Onieit (10), Oracit (1), Oricit (2), Omicit (1), Onieef (1), Orieit (1), Oureit (1), Ovicit (2), Ancet (1), Omcit (1), Omovit (1), [redacted] (1), [redacted] (3), Oniut (1), Onuit (2), and Onvit (1).*

C. SAFETY EVALUATOR RISK ASSESSMENT:

In reviewing the proprietary name [redacted], the primary concerns raised were related to four look-alike and/or sound-alike names: Oracit, Omnicef, Ansaid, and Emcyt.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that [redacted] could be confused with Oracit, a product that is currently marketed in the United States. One respondent from the written outpatient study interpreted the name to be Oracit. Additionally, two patients from the written outpatient study interpreted the name as [redacted] a phonetic variation of the name Oracit.

Oracit is an oral citrate solution that contains the active ingredients sodium citrate and citric acid. Oracit is used as a systemic and urinary alkalinizer, and is indicated for the treatment of metabolic acidosis, particularly when caused by renal tubular acidosis. It is also used in situations where long-term maintenance of alkaline urine is desirable. For example, in the treatment of patients with uric acid and cystine calculi of the urinary tract, and in conjunction with uricosurics in gout therapy, to prevent uric acid nephropathy. The recommended dose of Oracit is 15 to 30 mL diluted with water, taken after meals, and before bedtime. Oracit and [redacted] can sound similar when pronounced, and look similar when scripted (see page 6.) Additionally, both product names contain three syllables, and both have identical suffixes ('[redacted]

Oracit [redacted]

Oracit [redacted]

Oracit and [redacted] also share similarities in dosing. In pediatric patients, the recommended dose for Oracit is 5 mL to 10 mL after meals and at bedtime. [redacted] is administered in a dose of 0.25 mg (0.05 mg/mL) or [redacted] supplied in 5 mL vials intended for single dose intravenous administration. If route administration is omitted, it is possible that an in-patient order for [redacted] could be written with directions that read "give 5 mL now". If the prescription is written poorly, and the prescription order is misread, these directions would be considered within the recommended dosing for Oracit. If a patient mistakenly receives Oracit instead of [redacted] they would not only loose the anti-emetic effects of [redacted] but also be placed at risk for experiencing side effects associated with Oracit, such severe nausea, vomiting, or diarrhea, stomach pain, trouble breathing, and confusion or reaching thoughts. Additionally, patients could experience symptoms of hyperkalemia, which include listlessness, weakness, mental confusion, tingling of the extremities, and ECG abnormalities.

Omnicef contains cefdinir, a cephalosporin antibiotic, indicated for the treat of susceptible mid to moderate infections, including community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis, tonsillitis, uncomplicated skin and skin structure infections, and acute otitis media. The DMETS Expert Panel expressed concern that Omnicef and the proposed name, [redacted] may sound similar. Both names contain three syllables, with phonetically similar prefixes ("omni" vs. [redacted] Additionally, the endings of each name are similar as well, when pronounced ("cef" vs. [redacted] However, Omnicef and [redacted] differ in other aspects such as route of administration, dosage form, and strength. Omnicef is taken orally, and is available as a 300 mg capsule, and an oral solution with a concentration of 125 mg/mL [redacted] is given intravenously, and will be available as a single dose 5 mL vial in strengths of 0.25 mg (0.05 mg/mL), [redacted] Furthermore, [redacted] will be administered in-patient settings, and under the supervision of physicians and other health care providers who are experienced in the field of oncology.

Ansaid contains flurbiprofen, a non-steroidal anti-inflammatory drug, indicated for the treatment of rheumatoid arthritis and osteoarthritis. The DMETS Expert Panel expressed concern that Ansaid and the proposed name, [redacted] may sound similar. The beginnings of each name are similar when pronounced, and differ by only letter ("an" vs. [redacted]). Additionally the last syllable of each name is also phonetically similar ("said" vs. [redacted]). However, there are other factors that may decrease the potential risk of medication errors between Ansaid and [redacted] Ansaid and [redacted] differ in route of administration (oral vs. intravenous), and strength (50 and 100 mg tabs vs. 0.25 mg [redacted] single dose injection). Ansaid and [redacted] also differ in dosing regimen. Ansaid is taken daily in 2 to 4 divided doses, whereas [redacted] is given as a single dose approximately every 2 to 5 weeks. Given these differences in route of administration, strength, and dosing regimen the risk of confusion between the products is minimal.

Emcyt is a prescription only medication indicated for the palliative treatment of metastatic or progressive carcinoma of the prostate. The recommended daily dosage of Emcyt is 14 mg/kg/day in 3 or 4 divided doses, with a dose range of 10 to 16 mg/kg/day. The DMETS Expert Panel expressed concern that Emcyt and the proposed name, [redacted] might be confused, due to the identical pronunciation of the endings of each word ("—" vs. "cyt). However the beginnings of each name are different in sound and number of syllables, which clearly distinguishes the words from each other. Additionally, Emcyt is available as 140 mg capsule, which is taken in 3 to 4 divided doses, whereas [redacted] will be available as a 0.25 mg — single dose injection, given every 2 to 5 weeks. The differences in the drug names in addition to the differences in strength, dosage form, and dosing regimen, decrease the risk of confusion between Emcyt and [redacted]

III. COMMENTS TO BE PROVIDED TO THE SPONSOR:

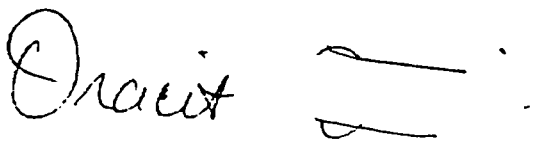
DMETS does not recommend the use of the proprietary name [redacted]

In reviewing the proprietary name '[redacted]', the primary concern raised was related to a look-alike name that already exists in the U.S. marketplace. The product considered having the greatest potential for name confusion was Oracit.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that [redacted] could be confused with Oracit, a product that is currently marketed in the United States. One respondent from the written outpatient study interpreted the name to be Oracit. Additionally, two patients from the written outpatient study interpreted the name as '[redacted]', a phonetic variation of the name Oracit.

Oracit is an oral citrate solution that contains the active ingredients sodium citrate and citric acid. Oracit is used as a systemic and urinary alkalinizer, and is indicated for the treatment of metabolic acidosis, particularly when caused by renal tubular acidosis. It is also used in situations where long-term maintenance of alkaline urine is desirable. For example, in the treatment of patients with uric acid and cystine calculi of the urinary tract, and in conjunction with uricosurics in gout therapy, to prevent uric acid nephropathy. The recommended dose of Oracit is 15 to 30 mL diluted with water, taken after meals, and before bedtime. Oracit and [redacted] can sound similar when pronounced, and look similar when scripted (see below). Additionally, both product names contain three syllables, and both have identical suffixes ("cit").

Oracit [redacted]



Oracit and [redacted] also share similarities in dosing. In pediatric patients, the recommended dose for Oracit is 5 mL to 10 mL after meals and at bedtime. [redacted] is administered in doses of 0.25 mg (0.05 mg/mL) [redacted] supplied in 5 mL vials intended for single dose intravenous administration. If route administration is omitted, it is possible that an in-patient order for [redacted] could be written with directions that read "give 5 mL now". If the prescription is written poorly, and the

prescription order misread, these directions would be considered within the recommended dosing for Oracit. If a patient mistakenly receives Oracit instead of [redacted] they would not only loose the anti-emetic effects of [redacted] but also be placed at risk for experiencing side effects associated with Oracit, such severe nausea, vomiting, or diarrhea, stomach pain, trouble breathing, and confusion or reaching thoughts. Additionally, patients could experience symptoms of hyperkalemia, which include listlessness, weakness, mental confusion, tingling of the extremities, and ECG abnormalities.

IV. RECOMMENDATIONS:

DMETS does not recommend the use of the proprietary name [redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
9/12/02 10:39:46 AM
PHARMACIST

Alina Mahmud
9/12/02 10:41:04 AM
PHARMACIST

Jerry Phillips
9/13/02 04:01:46 PM
DIRECTOR

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 4/9/02	DUE DATE: 7/9/02	ODS CONSULT #: 02-0068

TO: Victor Razckowski, MD,
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Brian Strongin,
Project Manager, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME:	**IND SPONSOR:** Helsinn Healthcare SA
Aloxi (Primary name) or [redacted] (Palonosetron Hydrochloride Injection) 0.25 mg (0.05 mg/mL) **IND#:** [redacted]	

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "Aloxi" and [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of proposed proprietary names Aloxi or [redacted] Please provide labels and labeling for safety evaluation upon receipt.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 7, 2002

IND# [redacted]

NAME OF DRUG: Aloxi or [redacted] (Palonosetron Hydrochloride Injection) 0.25 mg (0.05 mg/mL)

IND HOLDER: Helsinn Healthcare SA

***NOTE:** This review contains information that is provided by IMS Health; National Prescription Addit Plus (on-line) and is not to be used outside the FDA without prior clearance by IMS Health. A minimum of 2 weeks is required for clearance by IMS Health.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for an assessment of the proposed proprietary names Aloxi and [redacted] No safety assessment was made for the labeling of this product as no labeling is available at this time.

PRODUCT INFORMATION

Aloxi and [redacted] are the proposed proprietary names for Palonosetron Hydrochloride Injection. Palonosetron's proposed indication is for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherpy, including highly emetogenic chemotherapy. The recommended dosage is 0.25 mg [redacted] once daily in a single intravenous dose. This product is intended to be administered once per chemotherapy cycle, approximately every 2-5 weeks depending on the chemotherapy regimen. Aloxi [redacted] will be supplied as 0.05 mg/mL in a 5 mL vial

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look alike to Aloxi and [redacted] to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted six prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study for each proposed proprietary name, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Aloxi and [redacted] Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Aloxi. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in Table 2 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about either name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Aloxi	**Palanosetron HCl Injection 0.25 mg or 0.75 mg**	**0.25 mg in a single dose, Intravenously each chemotherapy cycle, approximately every 2-5 weeks.**	
Floxin	Ofloxacin Injection 400 mg/10 mL; 200 mg/50 mL; 400 mg/100 mL Ofloxacin Tablets 200 mg, 300 mg, and 400 mg	Injection: 200 mg to 400 mg every 12 hours. Tablets: 200 mg to 400 mg every 12 hours.	LA
Amoxil	Amoxicillin Capsules, USP 250 mg and 500 mg Amoxicillin Tablets, USP 500 mg and 875 mg Amoxicillin Tablets, USP (chewable), 125 mg, 200 mg, 250 mg and 400 mg Amoxicillin for Oral Suspension, USP 5 mL of reconstituted suspension contains125 mg, 200 mg, 250 mg, 400 mg	500 mg to 875 mg every 12 hours or 250 mg to 500 mg every 8 hours	SA

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Aloxi	**Palanosetron HCl Injection 0.25 mg or 0.75 mg**	**0.25 mg in a single dose, Intravenously each chemotherapy cycle, approximately every 2-5 weeks.**	
Adoxa	Doxycycline Monohydrate Tablets 50 mg and 100 mg	200 mg on the first day of treatment; follow with a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. Severe infections; 100 mg every 12 hrs.	SA/LA
Alora	Estradiol Transdermal System 0.05 mg/day; 0.075 mg/day; 0.1 mg/day	Apply twice a week.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
[redacted]	**Palanosetron HCl Injection 0.25 mg or 0.75 mg**	**0.25 mg in a single dose**	
Cinobac	Cinoxacin Capsules 250 mg and 500 mg	1 g/day, in 2 or 4 divided doses for 7 to 14 days.	SA
Cidex	Glutaraldehyde Solution 2% and 3.2%	Follow specific label directions for immersion to destroy vegetative pathogens on inanimate surfaces. Rinse equipment thoroughly before use.	SA/LA
Sinemet	Carbidopa Levodopa Tablets, USP SINEMET 25-100, containing 25 mg of carbidopa and 100 mg of levodopa. SINEMET 10-100, containing 10 mg of carbidopa and 100 mg of levodopa. SINEMET 25-250, containing 25 mg of carbidopa and 250 mg of levodopa.	Begin one tablet of Sinemet 25-100 three times a day. May increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of Sinemet 25-100 a day is reached. If Sinemet 10-100 is used, dosage may be initiated with one tablet three or four times a day. May increase by one tablet every day or every other day until 2 tablets four times a day is reached.	SA
			SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) *** Discovered after independent review			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Aloxi and [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 (Aloxi) and 107 [redacted] health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescriptions for Aloxi (below) and [redacted] see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

ALOXI

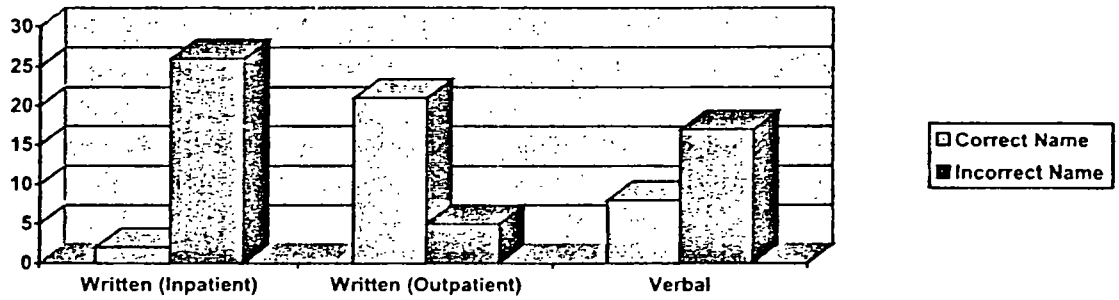
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Aloxi 0.75mg #2 UD	Aloxi 0.75 mg #2 As directed.
Inpatient RX: Aloxi 0.75 mg, X1	

2. Results:

The results for Aloxi are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) "Aloxi"	Incorrectly Interpreted (%)
Written Inpatient	39	28 (72%)	2 (7%)	26 (93%)
Written Outpatient	36	26 (72%)	21 (81%)	5 (19%)
Verbal	33	25 (76%)	8 (32%)	17 (68%)
Total	108	79 (73%)	31 (39%)	48 (61%)



Among participants in the written prescription studies, 31 of 54 respondents (57%) interpreted the name incorrectly. The interpretations were misspelled variations of "Aloxi". Incorrect interpretations of written prescriptions included: *Aloxe* (8 occurrences), *Aloxa* (3 occurrences), *Alox* (3 occurrences), *Altora, Altori, Aloxin* (2 occurrences), *Alexi, Alaxi,* and *Alax*. A currently marketed product, Alora appeared ten times among the incorrect interpretations.

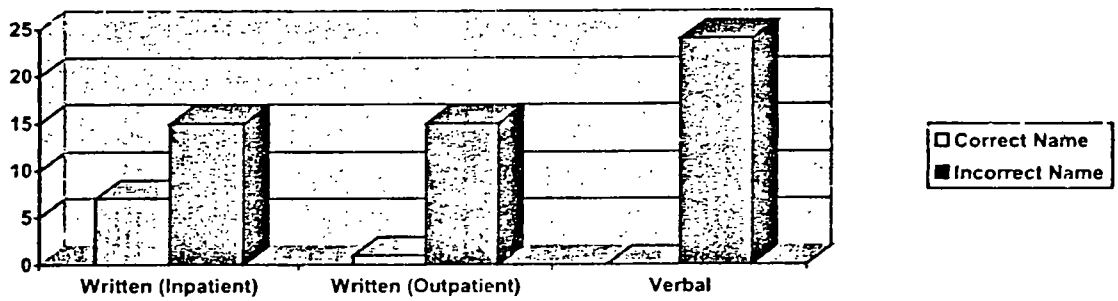
Among participants in the verbal prescription studies, 17 of 25 (68%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Aloxi". Incorrect interpretations of the verbal prescription included: *Aloxy* (7 occurrences), *Aloxie* (4 occurrences), *Alloxy, Alaxe, Iloxie, Alokvi, Alaxe,* and *Alloxe*.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: [illegible]: 0.25mg x 1	[illegible] 0.25 mg One Use as directed.
Inpatient RX: [illegible] 0.25mg x 1	

The results for [redacted] are summarized in Table II.

Table II

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) [redacted]	Incorrectly Interpreted (%)
Written Inpatient	36	22 (61%)	7 (32%)	15 (68%)
Written Outpatient	32	16 (50%)	1 (6%)	15 (94%)
Verbal	39	24 (62%)	0 (0%)	24 (100%)
Total	107	62 (58%)	8 (13%)	54 (87%)



Among participants in the written prescription studies, 30 of 36 respondents (83%) interpreted the name incorrectly. The interpretations were misspelled variations of [redacted] Incorrect interpretations of written prescriptions included: *Anvex* (4 occurrences), *Anirx*, *Anvix* (6 occurrences), *Cenvex* (2 occurrences), *Cenerx*, *Anvox*, *Cinvix*, *Cinnex* (8 occurrences), *Convex* (2 occurrences), *Cimvex*, *Connex*, *Cinrex*, and, *Annex*.

Among participants in the verbal prescription studies, 24 of 24 (100%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of [redacted] Incorrect interpretations of the verbal prescription included: *Sinvac*, *Simvex*, *Synvex* (11 occurrences), *Sinvex* (4 occurrences), *Synthec*, *Synbex*, *Synvec* (2 occurrences), *Simvax* [redacted] and, *Sinvax*. A currently marketed product, [redacted] appeared among the incorrect interpretations.

C. SAFETY EVALUATOR RISK ASSESSMENT

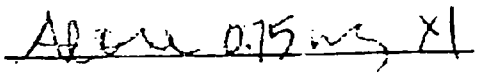
In reviewing the proposed proprietary name "Aloxi", the primary concerns raised related to look-alike, sound-alike confusion with names already in the U.S. marketplace. The products considered to have the greatest potential for name confusion with **Aloxi** were Floxin, Amoxil, Adoxa, and Alora. After reviewing the results of the study, an additional product [redacted] was identified. The products considered to have the ***greatest*** potential for name confusion with [redacted] were Cinobac, Sinemet and [redacted]

ALOXI

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that "Aloxi" can be confused with Alora. Study results for the written inpatient order for Aloxi included ten responses of "Alora". A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Alora (Estradiol Transdermal System) is indicated in:

- Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
- Treatment of vulval and vaginal atrophy.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

The usual dose is to apply a system twice a week. *Alora* and *Aloxi* may look similar when scripted. The writing sample used for the study is shown below. Please note how the letters "xi" look like the letters "ra". The drug products also share additional similarities. Alora is available in the strength, 0.075 mg/day, which is similar to the 0.75 mg strength of Aloxi. It is possible for an order written for "Alora 0.075 mg X 1" to be confused with an order for "Aloxi 0.75 mg X 1" and vice versa. It is also possible for dosing regimens to be confused for these two drug products since Alora is applied two times a week and Aloxi may be given every two weeks. Alora and Aloxi differ in route of administration and dosage form (transdermal patch vs. parenteral product for intravenous use). Because of the high potential for look alike confusion, there is potential for prescription errors between Aloxa and Alora despite the distinguishing features of the drug products. Inadvertent administration of Aloxi rather than Alora could result in estrogen treatment failure. If Alora were given instead of Aloxi, the patient would lose the antiemetic benefits of Aloxi and might experience the effects and side effects of estrogen therapy.



Floxin (Ofloxacin) is indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of microorganisms. The recommended dosage is 200 mg to 400 mg every 12 hours intravenously or orally (tablets). Floxin is available in 200 mg, 300 mg, and 400 mg tablets, in 40 mg/mL, 10 mL vials, and in 50 mL and 100 mL 4 mg/mL (200 mg), flexible containers. *Floxin* and *Aloxi* may look similar when written. The "Fl" in Floxin may look like the "A" in Aloxi (see writing sample on page 9). The only other distinguishing feature when comparing the scripting of these two names is the "n" in Floxin. It is possible that the "n" could trail off in a hurriedly written prescription. Floxin and Aloxi have other commonalties. Both drug products are available as injections for intravenous administration. However, Floxin and Aloxi differ in dosing regimen (every 12 hours vs. once every 2 to 5 weeks, respectively). They also differ in the strength 200 mg to 400 mg vs. 0.25 mg or 0.75 mg. Given the differences in strength and dosing regimen, the likelihood of confusion should be low.

Amoxil is a proprietary name for Amoxicillin. Amoxil is available as capsules, tablets, chewable tablets, and oral suspension. Amoxil is indicated in the treatment of infections due to susceptible (beta-lactamase-negative) strains of the microorganisms. The usual dosage is 500 mg to 875 mg every 12 hours or 250 mg to 500 mg every 8 hours. *Amoxil* and *Aloxi* may sound similar when spoken. Both names have three syllables. The first syllables "Am" vs. "Al" sound relatively similar combining the short "A" sound with a non-plosive* consonant. The second syllables "mox" vs. "lox" also sound very much alike. The last syllables "xil" vs. "xi" are somewhat distinctive but overall the names sound a lot alike perhaps because Aloxi has five of the six letters present in Amoxil. The products have other similarities. They have similar numeric strengths [250 mg (Amoxil) vs. 0.25 mg (Aloxi)]. Postmarketing experience has shown medication errors occurring as a result of a numerical similarity in strengths. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including route of administration, dosage form, dosing regimens, and lack of convincing sound alike properties.

Adoxa is a proprietary name for Doxycyline Monohydrate Tablets. Adoxa is indicated for the treatment of infections caused by susceptible strains of microorganisms. The usual dose is 50 mg or 100 mg every 12 hours. *Adoxa* and *Aloxi* may sound similar when spoken and may look similar when written. Both names have three syllables. The first syllables "Ad" vs. "Al" sound similar, combining the short "A" sound with similar sounding dental/alveolar consonants*. The second syllables "dox" vs. "lox" are likewise similar in sound. The last syllables "xa" vs. "xi" are somewhat distinctive in sound but overall the names sound alike. The names also look alike when scripted (see writing sample below). The names share the letters "A", "o" and "x". The "d" in Adoxa may look like the "l" in Aloxi as both letters have a prominent upstroke. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including route of administration, dosage form, strength, and dosing regimens.

[redacted]

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that [redacted] can be confused with Cinobac or Sinemet. The majority of interpretations from the written and verbal prescription studies were phonetic/ misspelled interpretations of the drug name [redacted] The names thought to have the greatest potential for confusion are discussed below.

* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html

Cinobac (Cinoxacin Capsules) is a quinolone antibiotic indicated for treatment of initial and recurrent urinary tract infections in adults caused by susceptible microorganisms. The usual recommended adult dose is 1 g/day, in 2 or 4 divided doses for 7 to 14 days. *Cinobac* and [redacted] may sound similar when spoken and look similar when written. The first syllables of each name "Cin" are identical. Although the rest of the names "obac" vs. ' — are distinctive, they do end with the similar sounding "c" and . Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on a lack of convincing sound alike similarities and differences between the medications including route of administration, dosage form, and dosing regimen.

Sinemet (Carbidopa Levodopa Tablets, USP) is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. The usual adult maintenance dose is Sinemet 25-100 or Sinemet 10-100, two tablets four times a day. *Sinemet* and [redacted] may sound similar when spoken. The first syllables of each name "Sin" vs. — are phonemes (spelled differently but sound exactly the same). The remaining portion of the names are somewhat distinctive. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on a lack of convincing sound alike similarities and differences between the medications including route of administration, dosage form, strength, and dosing regimen.

III. COMMENTS TO THE SPONSOR:

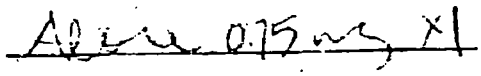
DMETS does not recommend the use of the proposed proprietary names Aloxi or [redacted]. We acknowledge the submission of a third proposed proprietary name, [redacted] will be the subject of another review. We will inform you of the acceptability of [redacted] at a later date.

ALOXI

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that "Aloxi" can be confused with Alora. Study results for the written inpatient order for Aloxi included ten responses of "Alora". A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Alora (Estradiol Transdermal System) is indicated in:

- Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
- Treatment of vulval and vaginal atrophy.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

The usual dose is to apply on system twice a week. *Alora* and *Aloxi* may look similar when scripted. The writing sample used for the study is shown below. Please note how the letters "xi" look like the letters "ra". The drug products also share additional similarities. Alora is available in the strength, 0.075 mg/day, which is similar to the 0.75 mg strength of Aloxi. It is possible for an order written for "Alora 0.075 mg X 1" to be confused with an order for "Aloxi 0.75 mg X 1" and vice versa. It is also possible for dosing regimens to be confused for these two drug products since Alora is applied two times a week and Aloxi may be given every two weeks. Alora and Aloxi differ in route of administration and dosage form (transdermal patch vs. parenteral product for intravenous use). Because of the high potential for look alike confusion, there is potential for prescription errors between Aloxa and Alora despite the distinguishing features of the drug products. Inadvertent administration of Aloxi rather than Alora could result in estrogen treatment failure. If Alora were given instead of Aloxi, the patient would lose the antiemetic benefits of Aloxi and might experience the effects and side effects of estrogen therapy.



[redacted]

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

IV. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

Please provide for evaluation upon receipt.

V. RECOMMENDATIONS:

DMETS does not recommend the use of the proprietary names Aloxi and [redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Charles Hoppes
7/16/02 12:57:00 PM
PHARMACIST

Carol Holquist
7/16/02 01:29:47 PM
PHARMACIST

Strongin, Brian K

From: Lehmann, Craig [craig@august-consulting.com]
Sent: Monday, June 30, 2003 6:53 PM
To: Brian Strongin (FDA) (E-mail)
Cc: Marie Kowblansky (FDA) (E-mail)
Subject: Proposed revised palonosetron product vial label, re NDA 21-372

Dear Mr. Strongin:

Please find attached a PDF file of the revised subject vial label. All the proposed vial label revisions are consistent with changes discussed and agreed with Dr. Kowblansky during the teleconference held earlier today and are revisions to the proposed vial label submitted earlier in NDA Amendment #012 dated June 25, 2003.

A copy of both pages of the attached PDF file - the same exact proposed revised vial label - will be submitted as NDA Amendment # 013 by FedEx tomorrow and will also be faxed to you at that time.

The following is our understanding of the revisions we and Dr. Kowblansky agreed upon during the teleconference. Each of the following proposed revisions are implemented in the attached PDF file revised vial label:

(1) We agreed to omit the sentence, "[redacted]" at the bottom of the previous vial label version since this is a single use use vial as already stated on the vial label.

(2) The NDC number was moved to the left margin of the newly created blank row above the word "Aloxi"

(3) The "Rx only" statement was moved to the right margin of the newly created blank row above the word "Aloxi"

(4) The following change was made to conserve vial label space to add items (5) and (6) below:

Change: [redacted]

To: "Dist. by MGI PHARMA, INC.

Bloomington MN 55437"

(5) "Store at 20°C-25°C (68°F-77°F)" was added to the space where the NDC number was.

(6) "Protect from light" was added to the space where "Rx only" was.

(7) Due to space limitations, it was agreed that the following statement will not be included on the vial label, "Excursions permitted to 15°C-30°C (59°F-86°F) (see USP)," since statement (5) above is more conservative, and the "Excursions permitted . . ." statement is on the carton label.

As agreed, a copy of the minutes of the teleconference citing all participants and including an explanation of all revisions agreed upon will be emailed to you tomorrow with a copy to Dr. Kowblansky.

Please advise me is you wish further information.

Best Regards,
Craig

<<450_016_VialLabel_Key_F.pdf>>

APPEARS THIS WAY
ON ORIGINAL

2 pages redacted from this section of the approval package consisted of draft labeling

FAX

August Consulting
515 Capital of Texas Hwy
Suite 150
Austin, Texas 78746
Tel: 512-347-1755
Fax: 512-347-9375

TO: Mr. Brian Strongin/FDA
FAX #: 301-443-9285
Phone: 301-827-7310
Date: June 25, 2003

FROM: Dr. Craig Lehmann
FAX #: 512-347-9375
Phone #: 512-347-1755

Re: **NDA 21-372**
Palonosetron Hydrochloride Intravenous Injection, 0.25 mg
Amendment # 0012
Chemistry, Manufacturing and Controls: Proposed revisions to immediate container (vial), carton and shipper labels
Sponsor: Helsinn Healthcare SA

Dear Mr. Strongin:

Please find attached a fax copy of the referenced NDA amendment which is scheduled to be FedExed to FDA today.

Please let me know if you wish further information. My phone number is 512-347-1755, fax 512-347-9375.

Sincerely,

FYI

Craig Lehmann, Pharm.D.
Authorized Representative for the NDA (ACI)

Cy: Dr. Dario Ceriani, Helsinn

August Consulting

515 Capital of Texas Highway
Suite 150
Austin, Texas 78746
Tel: 512.347.1755
Fax: 512.347.9375

June 25 2003

Robert L. Justice, MD, Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-372
Palonosetron Hydrochloride Intravenous Injection, 0.25 mg
Amendment # 012
Chemistry, Manufacturing and Controls: Proposed revisions to immediate container (vial), carton and shipper labels
Sponsor: Helsinn Healthcare SA

Dear Dr. Justice:

Provided in this amendment are proposed revisions to product vial, carton and shipper labels, as recently discussed with Mr. Strongin of your Division.

Please call me at 512-347-1755, if you wish additional information.

Sincerely,

Craig Lehmann, Pharm.D.
Authorized Representative for the NDA

cc: Dr. Dario Ceriani, Regulatory Affairs Senior Manager, Helsinn Healthcare SA
Mr. Franco DeVecchi Sr., Authorized US Corporate Representative (VPCI Inc.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-372

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
HELSINN HEALTHCARE SA	June 25, 2003
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
011-41-91-985-2121	011-41-91-985-2195
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* VIA PIAN SCAIROLO 6912 PAZZALLO (LUGANO) - SWITZERLAND	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Craig Lehmann, Pharm.D. August Consulting, Inc. 515 Capital of Texas Hwy., Suite #150 Austin, TX 78746 Tel #:(512) 347-1755, Fax #:(512) 347-9375

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
PALONOSETRON HYDROCHLORIDE (USAN name)	Aloxi™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
(3a*S*)-2[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride	08-PALO, RS-25259-197

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
5 mL vial	0.25 mg/5 mL	INTRAVENOUS

(PROPOSED) INDICATION(S) FOR USE:

osetron HCl is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeated es of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy.

PRODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Provides proposed revisions to product vial, carton and shipper labels.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

C...IFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
[signature]	Craig Lehmann, Authorized Agent for the NDA (ACI)	June 25, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
515 Capital of Texas Highway, Suite 150, Austin, TX 78746	(512) 347-1755

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
C... HFD-99
...ckville Pike
..., MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Proposed Revised Immediate Container (Vial) Label

The proposed revised vial label which follows is a revision to the proposed vial label submitted in the original NDA, Volume 1.7, page 218.

APPEARS THIS WAY
ON ORIGINAL

19 pages redacted from this section of the approval package consisted of draft labeling

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 24, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Latest Version of the Palonosetron Labeling Plus an Additional Sentence in the Clinical Studies Section.

Total no. of pages including cover: 3

Comments:

Here is the latest labeling as requested. In addition to the agreed-upon changes, we would like to add the following sentence to footnote C in Tables #1, #2, and #3 in the Clinical Studies section, "The studies were designed to show non-inferiority". The footnote will read as follows, " The studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between Aloxi and comparator." Thanks.

Document to be mailed: • YES ☑ NO

13 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Brian Strongin
7/24/03 02:25:37 PM
CSO

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

TRANSMISSION OK

TX/RX NO	2504
CONNECTION TEL	915123479375
CONNECTION ID	
ST. TIME	07/24 14:33
USAGE T	02'19
PGS. SENT	15
RESULT	OK

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 24, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Latest Version of the Palonosetron Labeling Plus an Additional Sentence in the Clinical Studies Section.

Total no. of pages including cover: 3

Comments:

Here is the latest labeling as requested. In addition to the agreed-upon changes, we would like to add the following sentence to footnote C in Tables #1, #2, and #3 in the Clinical Studies section, "The studies were designed to show non-inferiority". The footnote will read as follows, " The studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between Aloxi and comparator." Thanks.

Document to be mailed: • YES ☑ NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Revision to FDA Marked-Up Labeling for NDA 21-372 Faxed/E-Mailed 7/11/03

Total no. of pages including cover: 3

Comments:

A revision to the tables in the CLINICAL STUDIES section of the Palonosetron package insert is attached. We can discuss this during tomorrow's call. Thanks.

Document to be mailed: • YES ☑ NO

1 pages redacted from this section of the approval package consisted of draft labeling

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/s/

Brian Strongin
7/14/03 04:17:25 PM
CSO

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

TRANSMISSION OK

TX/RX NO	2475
CONNECTION TEL	915123479375
CONNECTION ID	
ST. TIME	07/14 16:29
USAGE T	00'44
PGS. SENT	3
RESULT	OK

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Revision to FDA Marked-Up Labeling for NDA 21-372 Faxed/E-Mailed 7/11/03

Total no. of pages including cover: 3

Comments:

A revision to the tables in the CLINICAL STUDIES section of the Palonosetron package insert is attached. We can discuss this during tomorrow's call. Thanks.

Document to be mailed: • YES ☑ NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 27, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Information request regarding vial label for NDA 21-372; Palonosetron

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: • YES ☑ NO

Regarding NDA 21-372 for Palonosetron HCL:

Please add the storage statement and a space for the lot number and expiration date to the proposed vial label.

Thanks.

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/s/

Brian Strongin
6/27/03 03:56:36 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 4, 2003

To: Craig Lehmann, Pharm. D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: August Consulting	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512) 347-1755	**Phone number:** (301) 827-7310

Subject: CMC Information Request for NDA 21-372, Palonosetron

Total no. of pages including cover: 2

Comments:

Please provide your response to these questions and comments ASAP. Thanks

Document to be mailed: ☐ YES ☑ NO

Please submit your response to the following comments and requests ASAP. Thanks.

Regarding Specifications

1. The proposed impurity limits listed below are too liberal when the manufacturing history and pivotal clinical batches are considered, as evidenced by the following data that you reported:

Please revise all individual and total impurity specification limits accordingly

2. Your use of the terminology "unspecified identified" for impurities — is confusing and inaccurate. You have set specifications respectively at — and — Please explain why specifications for these impurities are necessary when these impurities have not been detected in any of your drug product or drug substance batches. Also, please explain on what basis you have concluded that — is a potential degradation product when in fact it appears to be an —

3. Please be reminded that per ICH guidelines, impurities below 1 % should be reported to two decimal places.

4. The proposed — reporting threshold exceeds both the LOD and LOQ of the testing method. Please revise the — reporting threshold for impurities to reflect the experimentally determined LOD, with the understanding that these will be approximate values.

5. The specification for Bacterial Endotoxins should be lowered to reflect the manufacturing history.

Regarding Reference Standards

Please identify the sources of the palonosetron and — reference standards used in the — procedures and define the specifications to which they will conform.

Regarding Testing Procedures

1. All required testing methods for this product are covered under one method number, ——. —— Please identify each testing procedure with a unique identification number that would change when the method is modified.

2. The peak purity (vol. 5, page 134) for a stress-degraded palonosteron sample was shown to be only —— when analyzed with a photodiode array detector. Please provide evidence to demonstrate that there would not be this level of interference from impurities or degradants when evaluating the real-time stability of the product.

Regarding Stability

Please explain why impurity —— is reported to be —initially and then below the limit of detection at all time points through —— with the identical trend being reported for all three batches. A comparable trend is reported for total impurities with initial values of —— and all subsequent values of about —.

Regarding the Package Insert

To support the administration instructions given in the package insert, please provide data to demonstrate that the drug product remains stable for 24 hours when stored at refrigeration temperatures in a syringe.

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
6/5/03 08:29:18 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Statistical information request regarding NDA 21-372; Palonosetron

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Regarding NDA 21-372 for Palonosetron HCL:

1. Please provide a data set for each of studies PALO 99-03, -04 and -05 with the variables listed below.

   The data sets should contain the following information for each patient in the analysis (ITT) population:

   - Sequence number SEQ (=1,2,3,...N), indicating the order of allocation (so SEQ =1 for the first patient allocated to treatment, SEQ =2 for the second, etc.)
   - Patient ID
   - Values of stratifying variables (i.e., gender, chemotherapy history and use of corticosteriods where appropriate)
   - Imbalance score ("variance" for those assigned under the modified allocation) if patient were assigned to group A
   - Imbalance score ("variance") if group B
   - Imbalance score ("variance") if group C

   (For patients assigned under the original allocation scheme, the imbalance scores could be the simple counts of the group size that were used to determine assignment)

   - Tie ("balance")? Yes/No
   - Allocation scheme used (e.g., 1=pre-October 16, 2001, 2=minimum variance, 3=randomization due to balance, 4=randomization due to lack of kit)
   - Actual group assignment/treatment received

2. Please carry out a permutation test of the primary hypothesis in light of the allocation scheme, as described below; provide the results.

   The permutation test that we intended and would like you to perform should take into account (imitate) the actual randomization scheme. Only permutations of outcome values corresponding to a re-randomization of those patients randomized due to ties or need for alternative treatment kit should be considered. While smaller than the set of all possible permutations, the number of these permutations is still quite large. A random subset of these permutations may be chosen for technical feasibility, as you did in your original permutation test.

Please send ASAP.

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/s/

Brian Strongin

5/1/03 12:01:41 PM

CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Statistical information request regarding NDA 21-372; Palonosetron

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Regarding NDA 21-372 for Palonosetron HCL:

Confirm that the first allocation method used in studies PALO-99-03, -04 and –05, (until switched in October 2000) was stratified randomization. In addition, confirm that the second allocation method, begun in October 2000, was a minimization scheme as proposed by Taves and described in Scott et al. (Controlled Clinical Trials 23 (2002) 662-674). Otherwise, provide further details on the allocation methods used. In light of these allocation methods, clarify how a block size of 3 was implemented. Provide the number of cases of balance that were present under the second randomization scheme, i.e., the number of patients for which "a random number generator (was) …used to select one of the minimum variance treatment groups".

Please send ASAP.

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/s/

Brian Strongin
4/7/03 04:13:28 PM
CSO

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

TRANSMISSION OK

TX/RX NO	2180
CONNECTION TEL	915123479375
CONNECTIÓN ID	
ST. TIME	04/07 16:25
USAGE T.	00'20
PGS. SENT	3
RESULT	OK

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Statistical information request regarding NDA 21-372; Palonosetron

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 1, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7473

Subject: Statistical information request regarding NDA 21-372; Palonosetron

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Regarding NDA 21-372 for Palonosetron HCL:

1. Please indicate where the efficacy data for study PALO-00-01 (study 2330) can be found. If it has not been submitted, please do so.

2. Studies PALO-99-03, -04 and –05 all employed stratified randomization that was switched in October 2000 to a minimization scheme for allocation. In addition, if no drug kit of the selected study drug was available, an alternative procedure was followed. Please indicate how many and which patients were allocated under each of these three schemes in each study. Clarify if there is a variable that indicates date of randomization.

3. Please provide details of the permutation tests that were used as a "check for treatment allocation procedure." Specifically, a random sample "of all possible permutations was used for construction of the permutation distribution." Clarify if the set of "all possible permutations" was restricted in accordance with the actual procedure used for allocation of the patients. That is, under minimization the only randomness in allocation occurs for the first patient and subsequently when the two arms are "tied" and a random number generator is used to select between them; other assigments are completely determined by the values of the stratifying factors and thus all permutations in patient allocation are not possible.

Please send ASAP.

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/s/

Brian Strongin
4/1/03 05:48:42 PM
CSO

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Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 28, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7310
Subject: Clinical information request regarding NDA 21-372; Palonosetron	
Total no. of pages including cover: 2	

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 28, 2003

To: Craig Lehmann (US Agent)	**From:** Brian Strongin
Company: Helsinn Healthcare SA	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (512) 347-9375	**Fax number:** (301) 443-9285
Phone number: (512)347-1755	**Phone number:** (301) 827-7310

Subject: Pharm/tox information request regarding NDA 21-372; Palonosetron

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

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/s/

Brian Strongin
3/28/03 03:37:25 PM
CSO

Regarding NDA 21-372 for Palonosetron HCL:

1. In Study 99-03, the protocol states that if a patient is randomized to a drug and the clinical site does not have that drug available, the patient receives the drug the site does have. Clarify if patients who received a drug different from the drug they were randomized to because of lack of availability were considered protocol violations. If not, clarify how many times this occurred.

2. In Study 99-03 , the case report tabulation forms for Center 213 (Arkhangelsk) and several of the European sites were reviewed. They list the language on the diary card as being German, even in non-German speaking regions. Please explain the process for translation of the diary cards. Also please explain what the "language on diary card" parameter is in reference to. Clarify if this is the language that the patient communicated in.

Please send ASAP.

Regarding NDA 21-372 for Palonosetron HCL:

Please provide the historical control data for the mouse and rat carcinogenicity studies. The studies were conducted at . The data should be from the period from 1998 to 2001 and include the following:

1. all tumor incidences by organ,
2. data from individual studies
3. ranges for the period
4. average incidences.

The data should be only from studies of CD-1 mice and SD rats from the same supplier as those used in the carcinogenicity studies. Please send ASAP.

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/s/

Brian Strongin
3/28/03 02:56:10 PM
CSO