CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Administrative Documents

13.0 Patent Information Pursuant to 21 C.F.R. § 314.53

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355(b)(1):

TRADE NAME:	To be determined
ACTIVE INGREDIENT:	palonosetron hydrochloride
STRENGTH(S):	0.25 mg
DOSAGE FORM:	Injectable solution

In accordance with 21 C.F.R. § 314.53, the following information is provided for each United States patent that claims the drug product that is the subject of this NDA, a drug substance that is a component of such drug product, or a method of using such drug product, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product:

PATENT NUMBER:	5,202,333
DATE OF EXPIRATION:	13 April 2010
TYPE OF PATENT:	Drug substance, drug product (composition and formulation), and method of use *inter alia* for the prevention of chemotherapy-induced nausea and vomiting
NAME OF PATENT OWNER:	Syntex (U.S.A.) LLC

The undersigned declares that U.S. Patent Number 5,202,333 covers the drug substance palonosetron, formulations and/or compositions of palonosetron, and/or methods of using palonosetron. The drug product palonosetron is the subject of this NDA for which approval is being sought.

The undersigned certifies that the exclusive right and license to make, have made, develop, register, market, distribute, and sell palonosetron under U.S. Patent Number 5,202,333 is granted by the owner of the patent, Syntex (U.S.A.) LLC, to the applicant of this NDA, Helsinn Healthcare SA, under a licensing agreement between Syntex (U.S.A.) LLC and Helsinn Healthcare SA dated 23 June 1998.

Dario Ceriani

6th August 2002

Dario Ceriani
Senior Manager, Regulatory Affairs
Helsinn Healthcare SA

Date

6th August 2002

Matteo Missaglia
Director, Legal Affairs
Helsinn Healthcare SA

Date

EXCLUSIVITY SUMMARY for NDA # 21-372 SUPPL # N/A
Trade Name Aloxi™
Generic Name palonosetron HCl injection
Applicant Name Helsinn Healthcare S.A. HFD- 180
Approval Date July 25, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/ X/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X/

      If yes, what type(SE1, SE2, etc.)?

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

      YES / X / NO /___/

   d) Did the applicant request exclusivity?

      YES /___/ NO /x/

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

      YES /___/ NO / x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

   YES /___/ NO / x/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 1 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

{See appended electronic signature page}

Signature of Preparer — Date

Title: Brian Strongin, R.Ph., M.B.A.
Regulatory Health Project Manager
Division of GI and Coagulation Drug Products

{See appended electronic signature page}

Signature of Office or Division Director — Date

Title: Julie Beitz, M.D.
Deputy Director, ODE III

cc:
Archival NDA
HFD-180/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 21-372 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 9/26/02 Action Date: 7/25/03

HFD-180 Trade and generic names/dosage form: Aloxi™ (palonosetron HCl injection)

Applicant: Helsinn Healthcare S.A. Therapeutic Class: 5-HT_3 Receptor Antagonist

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ___ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ___	kg ___	mo. Birth	yr. ___	Tanner Stage ___
Max ___	kg ___	mo. < 1 month	yr. ___	Tanner Stage ___

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
  Adult studies ready for approval

- ☐ Formulation needed
- X Other: We will consider a waiver of pediatric studies for this age group if the Pediatric Rule is reactivated.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.** > 1 month	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** < 18 years	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): July 15, 2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: X Partial Waiver X Deferred ___Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo. Birth yr._____ Tanner Stage_____
Max_____ kg_____ mo. < 1 month yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
Adult studies ready for approval
☐ **Formulation needed**
☐ **Other: We will consider a waiver of the requirement for pediatric studies if the Pediatric Rule is reactivated.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.** > 1 month **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.** < 18 years **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): July 15, 2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Brian Strongin
7/21/03 04:25:45 PM

16 DEBARMENT CERTIFICATION

HELSINN HEALTHCARE SA

PALONOSETRON

16.0 Debarment Certification

Helsinn Healthcare SA hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Dario Ceriani

August 13th, 2002

Dario Ceriani
Senior Manager, Regulatory Affairs
Helsinn Healthcare SA

Date

Division Director Summary Review of a New Drug Application

NDA: 21-372
Drug: Aloxi™ (palonosetron hydrochloride 0.25 mg for injection)
Applicant: Helsinn Healthcare SA
Date: July 21, 2003

Palonosetron is a selective 5-HT_3 receptor antagonist which has been studied for use as an antiemetic with moderately and highly emetogenic cancer chemotherapy. The application was submitted on September 27, 2002. The applicant seeks approval of the following indications: (1) the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and (2) the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy.

Clinical Review

The clinical review was performed by Narayan Nair, M.D.. Two studies were submitted in support of each indication. Study PALO-99-03 is a multicenter, double-blind, active-controlled trial in 563 patients receiving moderately emetogenic chemotherapy. Patients were allocated to palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg administered intravenously 30 minutes prior to chemotherapy. Moderately emetogenic chemotherapy included carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2. The primary endpoint was the complete response rate in the first 24 hours. A complete response was defined as no emetic episode and no rescue medication. Non-inferiority to control therapy was prospectively defined as a lower limit of the 97.5% confidence interval for the difference in complete response rates (palonosetron – ondansetron) during the first 24 hours of greater than -15%. The results for the acute (0-24 hours) and delayed phases (24-120 hours) are shown below and were obtained from Table 14 of the Medical Officer Review by Dr. Nair.

Study PALO-99-03

Time Period (hours)	Number and percentage (%) Subjects with a Complete Response			Difference in CR rates, 97.5% Confidence Intervals	
	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Ondansetron 32 mg (N=185)	Pal. 0.25 mg minus Ond. 32 mg	Pal. 0.75 mg minus Ond. 32 mg
0-24	153 (81.0)	139 (73.5)	127 (68.6)	1.8%, 22.8%*	-6.1%, 15.9%
24-120	140 (74.1)	122 (64.6)	102 (55.1)	7.5%, 30.3%*	-2.4%, 21.3%

*$p<0.05$

These results show that palonosetron at a dose of 0.25 mg is superior to ondansetron in the acute and delayed phases. The palonosetron dose of 0.75 is non-inferior to

ondansetron in the acute and delayed phases. The applicant's recommended dose in the labeling is 0.25 mg.

Study PALO-99-04 is a second multicenter, double-blind, active-controlled trial in 569 patients receiving moderately emetogenic chemotherapy. Patients were allocated to palonosetron 0.25 mg, palonosetron 0.75 mg, or dolasetron 100 mg administered intravenously 30 minutes prior to chemotherapy. The primary endpoint, the definition of non-inferiority, and the definition of moderately emetogenic chemotherapy were the same as in study PALO-99-03. The results are shown in the table below and were obtained from Table 14 of Dr. Nair's review.

Study PALO-99-04

Time Period (hours)	Number and percentage (%) Subjects with a Complete Response			Difference in CR rates, 97.5% Confidence Intervals	
	Palonosetron 0.25 mg (N=189)	Palonosetron 0.75 mg (N=189)	Dolasetron 100 mg (N=191)	Pal. 0.25 mg minus Dol. 100 mg	Pal. 0.75 mg minus Dol. 100 mg
0-24	119 (63.0)	108 (57.1)	101 (52.9)	-1.7%, 21.9%	-7.7%, 16.2%
24-120	102 (54.0)	107 (56.6)	74 (38.7)	3.4%, 27.1%*	6.0%, 29.7%*

*$p<0.05$

In this study both doses of palonosetron were non-inferior to dolasetron in the acute phase and superior to dolasetron in the delayed phase. The results in the delayed phase confirm the finding with the 0.25 mg dose in study PALO-99-03.

Two studies were submitted in support of the highly emetogenic chemotherapy indication. Study PALO-99-05 is a multicenter, double-blind, active-control trial in 667 patients receiving highly emetogenic chemotherapy. Patients were allocated to palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg administered intravenously 30 minutes prior to chemotherapy. Highly-emetogenic chemotherapy included cisplatin ≥ 60 mg/m^2, cyclophosphamide > 1500 mg/m^2, and dacarbazine. The primary endpoint and definition of non-inferiority were the same as in the above studies. The results are shown in the table below and were obtained from Table 25 of Dr. Nair's review.

Study PALO-99-05

Time Period (hours)	Number and percentage (%) Subjects with a Complete Response			Difference in CR rates, 97.5% Confidence Intervals	
	Palonosetron 0.25 mg (N=223)	Palonosetron 0.75 mg (N=223)	Ondansetron 32 mg (N=221)	Pal. 0.25 mg minus Ond. 32 mg	Pal. 0.75 mg minus Ond. 32 mg
0-24	132 (59.2)	146 (65.5)	126 (57.0)	-8.8%, 13.1%	-2.3%, 19.2%
24-120	101 (45.3)	107 (48.0)	86 (38.9)	-4.6%, 17.3%	-1.9%, 20.0%

These results show that both doses of palonosetron are non-inferior to ondansetron.

Study PALO-00-01 is a randomized, Phase 2, double-blind, dose-ranging study in 161 patients receiving highly emetogenic chemotherapy consisting of either cisplatin ≥ 60 mg/m^2 or cyclophosphamide > 1100 mg/m^2. Patients were randomized to 0.3, 1, 3, 10, or 30 µg/kg day. However, in the analysis patients were placed in a fixed dose group of < 0.1 mg, 0.25 mg, 0.75 mg, 2 mg, or 6 mg. The primary endpoint was the complete response rate during the first 24 hours. The results were compared to a historical placebo group and are shown below (from Table 27 of Dr. Nair's review).

Study PALO-00-01, Complete Response in the First 24 Hours

	Historical Placebo	Palonosetron Dose				
		< 0.1 mg	0.25 mg	0.75 mg	2 mg	6 mg
N	70	30	27	24	27	46
CR, n (%)	6 (9%)	9 (30%)	12 (44%)	11 (46%)	15 (56%)	23 (50%)
p value	--	0.012	< 0.001	< 0.001	< 0.001	< 0.001

This study demonstrates that all doses are superior to the historical placebo and that doses higher than 0.25 mg do not provide substantially greater effectiveness.

In subgroup analyses by gender, the complete response rates for women were lower than for men in studies PALO-99-03, PALO-99-04, and PALO-99-05. This appears to be a class effect since it is also observed in the comparator arms. These analyses are summarized in the reviews by Drs. Nair and Korvick.

Adverse events occurring in ≥ 2% of patients in the chemotherapy-induced nausea and vomiting trials are listed in the applicant's table below. Since the 0.75 mg dose will not be used, this dose is not included in the table.

Adverse Events Occurring in ≥ 2%

Event	Palonosetron 0.25 mg (N=633)	Ondansetron 32 mg (N=410)	Dolasetron 100 mg (N=194)
Headache	9%	8%	16%
Constipation	5%	2%	6%
Diarrhea	1%	2%	2%
Dizziness	1%	2%	2%
Fatigue	< 1%	1%	2%
Abdominal pain	< 1%	< 1%	2%
Insomnia	<1%	1%	2%

Adverse events occurring at a rate of 1% included non-sustained tachycardia, bradycardia, hypotension and diarrhea. Adverse events occurring at a rate of < 1% included hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, superventricular extrasystoles, QT prolongation, allergic dermatitis, rash, motion sickness, tinnitus, eye irritation, amblyopia, dyspepsia, abdominal pain, dry mouth, hiccups, and flatulance. The sponsor notes that in many cases the relationship to palonosetron was unclear.

The potential for QT prolongation was reviewed by Drs. Nair and Korvick. The best ECG data was obtained from the phase 3 studies in which ECGs were collected at baseline and at 24 hours and 6-8 days after dosing. In addition, a subset of 193 patients (143 on palonosetron and 50 on an active comparator) had Holter monitoring two hours before to 22 hours after dosing and an ECG 15 minutes after dosing. The QTc data from the Phase 3 trials are shown below (modification of applicant's table 3.4.4:8 in volume 1.1, page 185). Although the ECG's were performed at different time intervals, each patient's worst QTc value is included in the table. The 15-minute ECG is closest to the expected C_{max}, and with a terminal half-life of 40 hours the 24-hour ECG's were performed at a time when there should have been substantial blood levels, particularly at the 0.75 mg dose. The data suggest that if palonosetron has clinically significant effects on QTc, the effects are similar to those of the approved drugs ondasetron and dolasetron. There is no evidence for a dose response effect on QTc for palonosetron in the Phase 3 studies or in the dose-ranging studies (data not shown). In an integrated analysis of all trials, the effect on QTcB or QTcB was 2 msec at both palonosetron doses and 4-5 msec for ondansetron and dolasetron.

Post-Dose Changes in QTc

	Palonosetron 0.25 mg N=594	Palonosetron 0.75 mg N=610	Ondansetron 32 mg N=404	Dolasetron 100 mg N=192
change in QTcB 30-60 msec	41 (6.9%)	54 (8.9%)	41 (10.1%)	13 (6.8%)
change in QTcB > 60 msec	5 (0.8%)	3 (0.5%)	7 (1.7%)	2 (1.0%)
QTcB >500 msec	1 (0.2%)	0 (0%)	1 (0.2%)	1 (0.5%)
change in QTcF 30-60 msec	27 (4.5%)	31 (5.1%)	32 (7.9%)	11 (5.7%)
change in QTcF > 60 msec	5 (0.8%)	2 (0.3%)	4 (1.0%)	1 (0.5%)
QTcF >500 msec	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

The Holter monitoring results are shown in Table 40, page 78, of Dr. Nair's review. The review states that "individual infrequent cases of Mobitz Type II block, sinus pauses, and occasional runs of nonsustained ventricular tachycardia were identified, however no difference in treatment groups was seen. Many of the subjects had underlying cardiopulmonary disease in addition to suffering from cancer and the physiologic stress of undergoing chemotherapy. Thus, there was a significant background rate of events but no clinically relevant difference seen between palonosetron at two different doses compared to ondansetron and dolasetron."

Statistical Review

The statistical review was performed by Stella Grosser, Ph.D. The review concluded that "there is sufficient evidence and reasonable certainty that palonosetron 0.25 mg is efficacious in the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer chemotherapy. This conclusion is based on standard statistical analyses, a permutation analysis that takes the actual allocation method in account, and a meta-analysis of historical results. While the analyses are based on comparisons to approved anti-emetics (ondansetron and dolasetron), the efficacy conclusions and claims are relative to placebo; the label should reflect this distinction."

"There is also sufficient evidence that it is efficacious in the prevention of delayed emesis following moderately emetogenic chemotherapy. Again, the analyses are based on comparisons to ondansetron and dolasetron, but the efficacy conclusions and claim are relative to placebo."

Clinical Inspection Summary

The assessment by the Division of Scientific Investigations was that "the clinical investigators that were inspected in support of NDA 21-372 did not adhere to the applicable regulations and good clinical practices governing the conduct of clinical investigations as noted herein. There were issues related to protocol deviation, inadequate and inaccurate recordkeeping, and inadequate informed consent. However, "in general, the inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, and completed subject diaries." The overall conclusion was that "the data submitted in support of this NDA appear to be acceptable."

Clinical Pharmacology and Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics review was performed by Sue-Chih Lee, Ph.D. and Suliman Al-Fayoumi, Ph.D. The review noted that "to evaluate the potential QT effect of palonosetron following IV administration, the sponsor analyzed 12-lead ECG data collected from Phase 3 trials in which palonosetron was studied at two dos levels (0.25 mg and 0.75 mg). A subset of the patients also received Holter monitoring. Based on the overall QT data and cardiac safety profiles, the QT effect of palonosetron appears to be similar to the approved comparator drugs (dolasetron and ondansetron) used in the trials. Palonosetron is eliminated through both renal excretion and metabolic pathways with the latter mediated via multiple CYP isozymes. *In vitro* studies indicated that it does not inhibit or induce the activity of many CYP isozymes at therapeutic concentrations. Therefore, the potential for drug interactions with palonosetron is low. No dosage adjustment is necessary based on age (18 years and up) or gender, nor is it necessary for any degree of renal or hepatic impairment. Safety and efficacy in pediatric patients have not been established." The review concluded that "the Human Pharmacokinetics and Biopharmaceutics section of the application is acceptable

provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the language in the package insert."

Chemistry Review

The chemistry review was performed by Marie Kowblansky, Ph.D. The recommendation of the 6/24/03 review was that the application may be approved pending completion of a satisfactory GMP inspection and "a written decision by the toxicology reviewer that impurities — are qualified to be present at the relatively high levels of —% as proposed by the applicant." The Division of Manufacturing and Product Quality gave an overall recommendation on July 14, 2003.

Microbiology Review

The microbiology review was performed by James L. McVey. The conclusion of his review was that "this application is recommended for approval from a product quality microbiology perspective."

Pharmacology/Toxicology Review

The pharmacology/toxicology review was performed by Yash Chopra, M.D., Ph.D. The overall recommendation was for approval of the application with changes in the labeling.

The review noted that " the cardiac physiology study with palonosetron showed that it prolonged action potential duration at concentrations of 0.3 and 3 μ M (100 and 1000 ng/ml). It inhibited maximal rate of depolarization at 3 and 30 μ M in rabbit Purkinje fibers. The cardiovascular studies with palonosetron indicated that it inhibited fast sodium and potassium channels (hERG (Ikr) and hHNa (Ina) currents) in HEK293 cells with IC_{50} of 1.9-2.04 μ M and 6.5 μ M, respectively. Palonosetron inhibited hERG current by ~17% at the lowest dose tested (10 ng/ml). This concentration was about 10.9 times the maximum plasma level (0.92 ng/ml) of palonosetron attained by the administration of an intravenous dose of 0.25 mg (5 μ g/kg if 50 kg body weight assumed) to subjects in clinical trials." The review also noted that "ondansetron also significantly inhibited the HERG currents in a dose dependent manner with an IC_{50} (1.8 μ M), similar to that of palonosetron." The cardiovascular effects of palonosetron on blood pressure, heart rate, and EKG were determined in conscious dogs. "The dogs were given palonosetron intravenously at 0.01, 0.1, and 1 mg/kg. Mean systolic and diastolic blood pressure, heart rate, and EKG were measured for 15 seconds at intervals of 15 minutes beginning 24 hours before and until 72 hours after dosing. No observed effects on these parameters were noted at doses up to the high dose of 1 mg/kg (20 mg/m^2). This dose is approximately 36 fold of clinical dose of 0.75 mg or 0.015 mg/kg if 50 kg body weight is assumed (0.56 mg/m^2)." In an anesthetized rabbit study, palonosetron at a dose of 10 mg/kg (120 mg/m^2) produced QT prolongation and ventricular tachycardia. Torsades de Pointes was not observed. However, the dose of 120 mg/m^2 is about 632 times the proposed dose of 0.25 mg (0.19 mg/m^2).

Dr. Chopra's memorandum of July 10, 2003 addressed the amounts of impurities present. The conclusion was that "the amounts of the impurities present in the clinical iv dose of 0.24 mg (5 ug/kg/day) palonesetron could be [redacted] ng/kg/day of [redacted] and [redacted] These are small fractions of safe doses of these compounds identified in these studies and support the proposed limit of the impurities."

The memorandum of July 10, 2003 by Jasti Choudary, B.V. Sc., Ph.D. provided specific recommendations for changes in the (1) Carcinogenesis, Mutagenesis, Impairment of Fertility, (2) Pregnancy and Pregnancy Category, (3) Nursing Mothers, and (4) OVERDOSAGES sections.

Pre-Approval Safety Conference

In the pre-approval safety conference with OPDRA it was agreed that the approval letter should ask the sponsor to submit as 15-day reports all cardiac events and cases of constipation. Cardiac events are of concern because of the potential for QTc prolongation. Constipation is of concern because it occurred in 5% of patients and because a healthy volunteer who received 0.75 mg in a Phase 1 trial experienced abdominal pain and constipation that required treatment in the emergency room.

Recommended Regulatory Action

1. Once the labeling negotiations have been completed, palonosetron should be approved for
   - the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and
   - the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.
2. The approval letter should state that the sponsor should submit all cardiac events and cases of constipation as 15-day reports.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

Robert Justice
7/21/03 06:50:46 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 25, 2003

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-372 Aloxi (palonosetron hydrochloride injection); Helsinn Healthcare S.A.

This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Drug Product's recommendation for approval of Aloxi, indicated for (1) the prevention of *acute* nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and (2) the prevention of *delayed* nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. Aloxi is a selective serotonin subtype 3 (5-HT_3) receptor antagonist and is currently not marketed in any country. The studies submitted under NDA 21-372 support approval for use of palonosetron 0.25 mg administered as a single intravenous dose 30 minutes before the start of chemotherapy.

Effectiveness: Comparative Claims

The original NDA was submitted September 26, 2002. Evidence that palonosetron 0.25 mg was effective in preventing *acute* nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy was demonstrated in three active-controlled, double-blind studies designed as non-inferiority studies. Two studies (PALO-99-03 and PALO-99-04) evaluated patients receiving moderately emetogenic chemotherapy and compared palonosetron to either ondansetron or dolasetron. The third study (PALO-99-05) compared palonosetron to ondansetron in patients receiving highly emetogenic chemotherapy. The primary endpoint for all studies was complete response rate defined as no emetic episodes and no rescue medications in the first 24 hours post-chemotherapy.

In two studies, palonosetron was found to be not inferior to the comparator, however in PALO-99-03 palonosetron was significantly better than the labeled dose of ondansetron. This finding is not replicated in other studies in the NDA and raised two concerns: (1) inclusion of this finding in labeling without an adequate disclaimer would imply that palonosetron is superior to ondansetron in preventing acute nausea and vomiting in patients receiving moderately emetogenic chemotherapy, and (2) exclusion of comparator drug names and doses would avoid a claim of superiority against the comparator drug but make interpretation of the study findings difficult. In labeling negotiations with the sponsor, it was agreed that comparator drug names and doses would appear in the Clinical Studies section along with the following disclaimer: "Clinical superiority over other 5-HT_3 receptor antagonists has not been adequately demonstrated in the acute phase."

PALO-99-03 and PALO-99-04 also provided evidence that palonosetron 0.25 mg was effective in preventing *delayed* nausea and vomiting in patients receiving moderately emetogenic chemotherapy, as defined as no emetic episodes and no rescue medications in the period 24-120 hours post-chemotherapy. In both studies, palonosetron was significantly better than labeled doses of the comparator. This was a critical finding from a regulatory standpoint since neither comparator drug is approved for prevention of *delayed* nausea and vomiting and their efficacy may be assumed to be similar to that of placebo. While these studies together support an indication for palonosetron for the prevention of *delayed* nausea and vomiting, the individual comparisons to ondansetron and dolasetron are not replicated in other studies in the NDA. Since it was desirable to not only include the comparator drug names and doses, but also avoid implying superiority claims against these drugs, the Clinical Studies section will state that palonosetron was effective in the prevention of *delayed* nausea and vomiting – not superior to a named drug or drug class.

In PALO-99-05, palonosetron was not significantly better than ondansetron in preventing *delayed* nausea and vomiting in patients receiving highly emetogenic chemotherapy. Again, the comparator is not approved for *delayed* nausea and vomiting and may be assumed to be similar to placebo. Therefore, a claim for *delayed* nausea and vomiting in patients receiving highly emetogenic chemotherapy is not tenable.

Effectiveness: Gender Effects

Although palonosetron 0.25 mg was effective in women for the indications under consideration, response rates were lower than for men. Similar trends have been noted for approved 5-HT_3 receptor antagonists. Too few palonosetron-exposed women were evaluated pharmacokinetically to definitively conclude there were no gender differences in pk parameters. However, response rates in women who received three times the recommended dose of palonosetron (i.e., 0.75 mg) in controlled studies were not consistently higher than response rates on 0.25 mg. Further pharmacokinetic evaluation of palonosetron-treated women will not be requested at this time.

Safety

The most common adverse events seen with palonosetron were constipation and headache, occurring with an incidence of 5% and 9% respectively. These occurred at frequencies similar to that observed with the comparator 5-HT_3 receptor antagonists.

Patients enrolled in the three controlled studies were evaluated prospectively for evidence of QT prolongation. When the data from these studies were pooled, the mean QTc change from baseline was 2 msec for palonosetron 0.25 mg (using either Bazett or Fridericia correction methods) compared to a mean QTc change of 4-5 msec for patients on the ondansetron and dolasetron arms. Small numbers of outliers (i.e., patients with a mean QTc change > 60 msec or a QTc value > 500 msec) were noted on the palonosetron and comparator arms with similar frequency. There were no reports of torsade de pointes. Labeling will include a Precaution for use in patients at risk for the development of QT prolongation. Further evaluation of QTc does not appear warranted at this time.

Tradename Review

The proposed tradename "Aloxi" is acceptable.

Phase 4 Studies

There are no phase 4 study commitments for this product.

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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

/s/

Julie Beitz
7/25/03 08:31:03 AM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 7/7/03

FROM: Joyce A Korvick, MD, MPH **(Deputy Director)**

DGCDP/ODE III

SUBJECT: **Acting Team Leader Summary Approval Comments**
NDA 21-372

APPLICANT: Helsinn Healthcare SA

DRUG: Palonosetron 0.25 mg for injection
(5HT3 receptor antagonist)

REGULATORY RECOMMENDATIONS:
The GI Team recommends that this application be approved for the following indications:

- **the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and**
- **the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.**

I. Background:
Palonosetron was initially developed by Syntex Laboratories Inc. The first Investigational New Drug (IND) clinical protocol (IND) was submitted on June 2, 1992.

Syntex

(IND). Between 1992 and 1995 Syntex conducted 5 Phase 1 trials and 5 Phase 2 trials for both the oral and intravenous formulation of palonosetron.

In 1998, Helsinn Healthcare AS (based in Lugano, Switzerland) acquired palonosetron from Syntex Laboratories. On June 23, 1998, all rights and responsibilities related to IND's (IV palonosetron), and were transferred.

An End-of Phase 2 Meeting between Helsinn and the FDA was held on March 10, 1999, and a follow-up teleconference was held April 29, 1999. At that time a concern as to whether palonosetron was metabolized to (a metabolite with potential

cardiovascular toxicity) was raised. In response to these concerns, a series of *in vitro* and *in vivo* metabolic studies were conduced by Helsinn that demonstrated that this metabolite was not present. In late 1999, Helsinn submitted pivotal efficacy protocols for Special Protocol Assessment. The FDA replied to these with the following pertinent points: 1.) agreed with the definition of the primary efficacy endpoint "complete response"; 2.) agreed to the uses of concomitant dexamethasone; 3.) suggested a subset of patients would undergo Holter monitoring (approximately 300, the applicant agreed and conducted the studies).

Clinical trials PALO-99-03 and PALO-99-04 involved moderately emetogenic chemotherapy and PALO-99-05 involved highly emetogenic chemotherapy. To support a claim for palonosetron in the prevention of chemotherapy induced nausea and vomiting (CINV) due to highly emetogenic chemotherapy, the agency agreed with the applicant's plan to use Study PALO-99-05 (a comparison of palonosetron to ondansetron and historical control) and Study 2330 (a Phase 2 efficacy, safety, and pharmacokinetics trial). In October of 2001 the Agency raised statistical concerns in the Special Protocol Assessment. There were no historical placebo complete response efficacy data regarding placebo use with dexamethasone for acute CINV. The applicant suggested using meta-analysis to predict the dexamethasone effect on historical placebo and the agency agreed that may be the best approach.

There are currently three approved 5HT3 receptor antagonists approved for use in the US. They all have been shown to affect ventricular depolarization and repolarization, no significant safety concerns have been introduced regarding this pharmacologic class since their introduction into the market. The following is a list of these agents and their approved CINV indications as listed in the approved drug labels.

Zofran (ondansetron injection): Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose beyond 24 hours in these patients has not been established.
Kytril (granisetron injection): is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
Anzemet (dolasetron injection): the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin

II. Discipline Review summary and commentary:

A. OPDRA/DDMAC/DMETS:

DDMAC labeling comments suggest addition of potential hypersensitivity reactions in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists. This is an important recommendation with which clinical agrees.

DMETS rejected the names [redacted] and [redacted] DMETS did agree with the approval of the name Aloxi if the 0.75 mg strength is not marketed, which is the case.

B. Chemistry:

The chemistry review was completed (6/24/03) and palonosetron was found to be approvable upon resolution of the following issues:

1.) Completion of satisfactory GMP inspection
2.) A written decision by the toxicology reviewer that impurities [redacted]

are qualified to be present at relatively high levels of [redacted]%, as proposed by the applicant.

Based upon the 18-month primary stability data, a 24-month expiration is appropriate for the product at the present time. Microbiology review finds this drug product acceptable for approval.

C. Phamacology/Toxicology:

The potential for cardiac effects due to palonosetron was explored in several ways in pre-clinical studies. There was an effect seen in the hERG model. The results indicated that palonosetron significantly inhibited hERG tail currents in a concentration dependent manner with IC50 of 2.04 μM. At the lowest concentration tested 10ng/ml, the hERG tail currents were inhibited by approximately 17%. Ondansetron was studied and was shown to significantly inhibit the hERG tail currents in a dose dependent manner as well, with an IC 50 (1.8uM) is similar to that of palonosetron.

In vitro electrophysiological effects of palonosetron were assessed in canine Purkinje fibers. There was prolongation of the action potential consistent with the hERG data. Further exploration of the cardiac effect was undertaken in the conscious dog model. No observed effects on ECG, diastolic blood pressure, or heart rate were seen at doses up to the high dose of 1 mg/kg (20 mg/m^2). This dose is approximately 36 fold higher than the clinical dose of 0.75 mg. Pro-arrhythmic activity of palonosetron and ondansetron as studied in anaesthetized rabbits. Polymorphic tachycardia was not seen in these animals.

In conclusion palonosetron demonstrated an effect of on the QT interval, however, the doses tested represent a reasonable safety margin and several of the results were comparable to approved 5HT3 agents.

D. Biopharmaceutics:

The Biopharmaceutics review as completed on 6/24/03 and found the application acceptable. Palonosetron is eliminated through both renal excretion and metabolic pathways. *In vitro* studies indicated that it does not inhibit or induce the activity of many CYP isozymes at the therapeutic concentrations. Therefore the potential for drug interactions with palonosetron was considered to be low by the biopharmaceutics reviewers. No dosage adjustment is necessary based on age (18 years and up) or gender, nor is it necessary for any degree of renal or hepatic impairment.

Data from phase 1 and 2 studies was summarized into a single analysis to explore a dose-response relationship. The applicant concluded that there was no dose response relationship. However, the timing of the ECGs post-dose was in adequate to definitively state that there was no dose response seen in patients. Patients did receive up to 90ug/kg dose and had no adverse cardiac effects. This dose is equivalent to 6.3 mg of palonosetron, 25 times greater than the recommended dose. The biopharmaceutics reviewers went on to comment that the dose-response data is limited in its usefulness due to the fact that the ECG data was not monitored more frequently after the administration of palonosetron. They suggested that the final analysis of safety related to cardiac effects of palonosetron be made based upon the findings in the clinical review. The level of concern regarding potential ECG effects, according to the biopharmaceutics reviewer, is not as high as it might be due to the fact that this drug is being given in a single dose, it has both renal elimination and hepatic metabolism by multiple pathways, and it is similar in its effect to other drugs in its class. It was suggested that analysis of the phase 3 ECG data would be important to fully evaluate the clinical significance of the QT effect.

To evaluate the potential QT effect of palonosetron following single IV administration, the sponsor analyzed 12-lead ECG data collected from Phase 3 trials in which palonosetron was studied at two dose levels (0.25 mg and 0.75 mg). A subset of the patients also received Holter monitoring. Further comment on these data are made in the clinical section, however, in general the effect appeared to be similar to the approved comparator drugs (dolasetron and ondansetron) used in the clinical trials.

Initially, there was a concern regarding the effect of the major metabolites, M9 and M4. These metabolites had negligible pharmacological activity. A suspected compound, ——— existing as a related impurity of the drug substance, was studied. A ——— method was used to detect the presence of ——— and its metabolite ——— in human plasma and urine samples. This study showed that palonosetron is not metabolized to ——— in man.

E. Clinical Efficacy/Safety:

EFFICACY

Statistical:

The primary area of statistical concern included the minimization allocation procedure used in the pivotal studies PALO-99-03, -04, -05, and the agreed upon delta in studies that did not have placebo controlled arms. Because the standard statistical tests and confidence interval calculations make the assumption of random allocation, there was concern about the evaluation of the results using the minimization allocation procedure used by the applicant. Permutation methods were used to test the conclusions. The results of the testing supported the conclusion of efficacy.

None of the efficacy trials included a placebo control. To assess trial validity and the justification of the value of delta used to declare non-inferiority of

palonosetron to ondansetron or dolasetron, an examination and meta-analysis results from the anti-emetic literature were carried out. The statistical reviewer concluded that the magnitude of the differences found or modeled in the meta-analysis were large enough to justify a conclusion of non-inferiority of palonosetron in the current trials.

The primary efficacy results are listed below (the confidence intervals included are at the 97.5% level):

Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-03

Palonosetron 0.25 mg		Palonosetron 0.75 mg		Ondansetron 32 mg	
Proportion	CI	Proportion	CI	Proportion	CI
153/189(81%)	75, 86	139/189(74%)	67, 80	127/185(69%)	61, 75

Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-04

Palonosetron 0.25 mg		Palonosetron 0.75 mg		Dolasetron 100 mg	
Proportion	CI	Proportion	CI	Proportion	CI
119/189(63%)	56, 70	108/189(57%)	50, 64	101/191(53%)	46, 60

Proportion of patients achieving a complete response (CR) during the first 24 hours after chemotherapy, study PALO-99-05

Palonosetron 0.25 mg		Palonosetron 0.75 mg		Ondansetron 32 mg	
Proportion	CI	Proportion	CI	Proportion	CI
132/223(59%)	52, 66	146/223(66%)	59, 72	126/221(57%)	50, 64

The difference in the confidence intervals is as follows:

Confidence intervals for the difference between the palonosetron doses and the comparators in complete response rates during the first 24 hours after chemotherapy, standard analysis

	Palonosetron 0.25 vs. Ondansetron	Palonosetron 0.75 vs. Ondansetron	Palonosetron 0.25 vs. Dolasetron	Palonosetron 0.75 vs. Dolasetron
99-03	2, 23	-6, 16		
99-04			-2, 22	-8, 16
99-05	-9, 13	-2, 19		

In all cases the lower limit of the 97.5% CI was above –10%, implying a reasonable certainty that the proportion of complete responders to palonosetron was no more than 10% less than the proportion among the comparators. In the case of ondansetron vs palonosetron 0.25 mg the difference was above zero indicating superiority.

The comparators are not approved for the prevention of delayed nausea and vomiting, a secondary endpoint. In a previous discussion with the applicant, the division concluded,

that if palonosetron were superior to a non-approved indication, this would be sufficient to warrant that indication. For moderately emetogenic chemotherapy the results were statistically significant for prevention of delayed nausea and vomiting when compared to either dolasetron or ondansetron (lower limit of the confidence interval was above zero for both studies). The results were not statistically significant for highly emetogenic chemotherapy.

Clinical:
The clinical reviewer is in agreement with the statistical review. The Complete Response between 24-120 hours after chemotherapy was felt to be a clinically meaningful endpoint by the primary reviewers and this team leader. Even though the exact definition of delayed response was not pre-specified, the analyses that support this were. Therefore, consideration of the indication for prevention of delayed nausea and vomiting was deemed appropriate. The results were as described above.

SAFETY:
Clinical:
The safety profile for palonosetron was similar to that of the comparators studied (ondansetron and dolasetron). The most frequent adverse events are displayed below. In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron 0.25 mg.

Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Palonosetron 0.25 mg (N=633)	Ondansetron 32 mg IV (N=410)	Dolasetron 100 mg IV (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

Two subjects experienced severe constipation following a dingle palonosetron dose of approximately 0.75-mg, three times the recommended dose. One patient received a 10 µg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75-mg IV dose in a pharmacokinetic study. These resolved without serious sequelae.

Cardiovascular Adverse events: 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to palonosetron was unclear.

Further detailed exploration into the effect of palonosetron on the QT interval was undertaken. In the Phase III trials, the mean change from baseline QTc ranged from -1 to +3 msec without any dose trends and without any case of major change from baseline. When all the Phase 3 ECG data was pooled, the effect on the QTc parameter by Bazett or Fridericia correction was 2 msec at both palonosetron doses. In the comparator arms the QTc mean changes from baseline were larger (4-5 msec). There were a few cases of new absolute QTcB or QTcF >500 msec but these were equally distributed in all treatment arms.

Review of the ECG data regarding QTc by Frederica or Bazett Corrections revealed the following information (24 hour post-dose):

	Palonosetron 0.25 mg (N =605) Nt = 594		Palonosetron 0.25 mg (N =610) Nt = 601		Ondansetron 32 mg (N = 410) Nt = 404		Dolasetron 100 mg (N = 194) Nt = 192	
	N	%	N	%	N	%	N	%
Delta QTcB 30 to 60 msec	41	6	54	9	41	10	13	6
Delta QTcB > 60 msec	5	0.8	3	0.5	7	1	2	1
QTcB >500 msec	1	0	0	0	1	0	1	0
Delta QTcF 30 to 60 msec	27	4	31	5	32	7	11	5
Delta QTcF > 60 msec	5	0.8	2	0.3	4	1	1	0
QTcF >500 msec	0	0	0	0	0	0	1	0

Nt= number treated

It should be noted that patients with cardiac abnormalities were not excluded from the studies.

There is some question about the timing of the collection of the ECG after the dose. An ECG was taken before dosing and after 24 hours. Given that this is a single intravenous injection, it is of more interest to analyze the ECGs that were recorded more closely in time to the administration of the test drug. The optimal timing of the ECG is unknown due to the fact that the maximal pharmacodynamic effect of palonosetron on the QT interval may not occur at the same time as the Cmax. In order to explore this further,

patients who had Holter monitoring were studied. In this group of patients a routine ECG was performed at 15 minutes post dose. This data is displayed in the table below.

Holter monitor patients ECG results at 15 minutes post-dose

Changes from Baseline	Palonosetron 0.25 mg N=60 (%)	Palonosetron 0.75 mg N=62 (%)	Ondansetron 32 mg N=40 (%)	Dolasetron 100 mg N=6 (%)
Delta QTc 30 to 60 msec	9 (15)	3 (5)	8 (20)	1 (17)
Delta QTc > 60 msec	0 (0)	1 (2)	0 (0)	0 (0)
Delta QTcB 30 to 60 msec	5 (8)	3 (5)	8 (20)	1 (17)
Delta QTcB > 60 msec	0 (0)	0 (0)	0 (0)	0 (0)
Delta QTcF 30 to 60 msec	4 (7)	4 (7)	5 (13)	1 (17)
Delta QTcF > 60 msec	0 (0)	0 (0)	0 (0)	0 (0)

In addition to the above data, none of these patients with a normal baseline QT (<500 msec) had a QT measurement post dose of >500 msec.

Among the Holter patients, the uncorrected delta QTc of 30-60 msec was seen in from 5-20% of patients in all groups. It is of interest to note that the higher dose of palonosetron had a lower percentage of patients with this delta (5%). Uncorrected, only one patient in the 0.75 mg palonosetron group had a delta QTc of >60 msec. Both Fredericia and Bazett's corrections have lower incidences of patients in the delta QTc 30- 60 msec range. The lowest percentage occurred in the palonosetron treatment groups as compared to the control drug groups. Only one of the Holter monitor patients had a delta QTc > 60 msec when this interval was corrected by Fredericia or Bazett's methodology (a 0.25 mg dose). Finally, the actual Holter data do not show a signal that palonosetron induces clinically relevant supraventricular or ventricular arrhythmias, including Torsades des Pointes, or atrio-ventricular conduction defects.

The cardiac profile for this drug appears to be similar to the other 5HT3 antagonists. It is a single dose therapy, with multiple pathways for elimination and metabolism, therefore it is not expected to accumulate. There was not definitive clinical data that rule out a dose-effect correlation between palonosetron and QT. However, this drug was administered in higher doses than proposed for approval. Therefore, the reviewers conclude that while there is a QT effect, it does not pose a major safety risk and as such it can be approved with appropriate labeling.

SPECIAL POPULATIONS:

Gender: Overall, there was a higher in response rates in males compared to females. Both rates were comparable to the comparator arms and both rates were effective. There was an insufficient number of women studied in the pharmacokinetics portion of the NDA to determine if this effect was related to dose. However, in the phase 3 studies two

doses of palonosetron were studied. There was no apparent dose effect seen in these studies for moderately emetogenic chemotherapy(see table below).

Number and Percentage of Complete Responses by Gender

Study 99-04 (Moderately Emetogenic Chemotherapy)									
	Palonosetron 0.25 mg N = 189			Palonosetron 0.75 mg N = 189			Dolasetron 100 mg N = 191		
	N	N*	%	N	N*	%	N	N*	%
Male	34	30	88.2	33	21	63.6	35	22	62.9
Female	155	89	57.4	156	87	55.8	156	79	50.6
Study 99-03 (Moderately Emetogenic Chemotherapy)									
	Palonosetron 0.25 mg N = 189			Palonosetron 0.75 mg N = 189			Ondansetron 32 mg N = 185		
	N	N*	%	N	N*	%	N	N*	%
Male	54	49	90.7	51	46	90.2	52	41	78.8
Female	135	104	77.0	138	93	67.4	133	86	64.7
Study 99-05 (Highly Emetogenic Chemotherapy)									
	Palonosetron 0.25 mg N = 223			Palonosetron 0.75 mg N = 223			Ondansetron 32 mg N = 221		
	N	N*	%	N	N*	%	N	N*	%
Male	108	72	66.7	110	75	68.2	108	73	67.6
Female	115	60	52.2	113	71	62.8	113	53	46.9

N = number or male or female patients
N* = number of patients with complete response

In one study of highly emetogenic chemotherapy, the response in females was lower than males. Additionally, an approximately 10% difference in efficacy was seen in females comparing the 0.25 mg and 0.75 mg doses. However, both of these does were effective as compared to ondansetron. If the applicant wished to optimize the dose in women given highly emetogenic chemotherapy, given the potential for possible cardiac side effects, the applicant would have to perform additional pharmacokinetic studies in women due to the limited amount of such data available in women.

F. Labeling Comments:

See FAX July 10, 2003.

Considerations:

1. Comparator names efficacy and safety sections: advised to leave them in the label. This is for several reasons, first and foremost because it makes the results understandable to the clinician. Secondly, the delayed claim did demonstrate superiority over the comparators, and these are deemed to be similar in activity, neither being approved for this indication. Third, for the acute claim,

there was one study that demonstrated superiority, the others demonstrated non-inferiority. Because only one study demonstrated superiority over an approved drug/indication a disclaimer was proposed in the label. The names of the competitors remain in the label for this indication, but the disclaimer clearly states that superiority was not demonstrated for the acute claim. Thus, clearly blocking advertising of superiority for either comparator for the acute indication.

1. **Not studied in pediatric patients:** this should be clearly stated in the label.

2. **Gender effect:** the difference in effect it is not felt to be clinically significant to warrant inclusion in the label. It is effective in women.

3. **QT effect: the** label should include some information about the clinically relevant information regarding the effect of palonosetron on the potassium channels. The fact that there is a small effect, that it appears to be similar to the other approved agents, Torsades de Pointe was not documented among these patients and only 1 patient in the 0.25 mg group with a normal baseline ECG had a post-dose QT measurement of >500 msec.

G. **Phase 4 commitments:** at this time there are none. Refer to the approval letter for final recommendations.

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

/s/

Joyce Korvick
7/21/03 06:46:30 PM
MEDICAL OFFICER

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 11, 2003

TIME: 2:15 PM - 2:30 PM

LOCATION: Diane Moore's Office; Room 6B-45 (Parklawn)

APPLICATION: NDA 21-372; Palonosetron® (hydrochloride) Injection, 0.25 mg

TYPE OF MEETING: Telecon; Advice

MEETING CHAIR: Dr. Sue Chih Lee

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)

Diane Moore, Regulatory Health Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)

Sue-Chi Lee, Ph.D. - Biopharmaceutics Reviewer

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

August Consulting

Dr. Craig Lehmann, agent for NDA sponsor, Helsinn Healthcare, S.A.

BACKGROUND:

The study compound converts to a cardiotoxic substance *in vivo*.

MEETING OBJECTIVE:

To obtain clarifications regarding Study PALO-02-01.

DISCUSSION POINTS:

- The FDA Pharmacokinetics reviewer requested clarification regarding data presented in Study PALO-02-01 entitled, "The Metabolism of [^{14}C]-Palonosetron in Human Hepatic Microsomes, Cryopreserved Hepatocytes and Fresh Liver Slices-Investigation of the Conversion of [^{14}C]-Palenosetron to [redacted] submitted to the original NDA on September 26, 2002 (received September 27, 2002). In the chromatograms in Volume 1.75 (page 56 and 61), the upper graph (Figure 7) shows the control without NADPH. The peak for Palonosetron is the same height in the next figure. It appears that nothing was metabolized after 60 minutes of incubation with Palonosetron. The Division requested the sponsor submit the following:

1. Supporting data that demonstrates how much of Palonosetron is metabolized after 60 minutes, and

2. A magnified chromatogram so that any ———formation may be observed.

- Additional data is also requested to address the same situation in Volume 1.75 on pages 61 and 66. Although the systems differ, the graphs are similar.

- The above information is needed to interpret Table 3 in Volume 1.75 on Page 49 as well.

Action Items:

The representative will relay the Agency's request to the NDA sponsor.

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

drafted: dm
revised: S.C.Lee 7.3.03
initialed: S.C.Lee 7.3.03
Corrected: July 7, 2003
Finalized: July 7, 2003
Filename: N21372TC61103.doc

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

/s/

Diane V. Moore
7/7/03 05:27:42 PM

Sue Chih Lee
7/7/03 05:30:25 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 10, 2002

Time: 11:00AM

Location: Parklawn Building Conference Room B, Third Floor

Application: IND[redacted]Palonosetron HCL Injection

Type of Meeting: Type B; Pre-NDA

Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D.

Meeting Recorder: Brian Strongin, R.Ph., M.B.A.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader, GI Drugs
Robert Prizont, M.D.	Medical Officer
Jasti Choudary, B.V.Sc., Ph.D.;	Supervisory Pharmacologist
Eric Duffy, Ph.D.	Director, Office of New Drug Chemistry II
Liang Zhou, Ph.D.;	Chemistry Team Leader
Joe Sieczkowski, Ph.D.	Review Chemist
Brian Strongin, R.Ph., M.B.A.	Project Manager

Division of Biometrics III

Tom Permutt, Ph.D.; Statistical Team Leader

External Constituent Attendees and Titles:

Helsinn Healthcare SA

Dr. Dario Ceriani	Senior Manager Regulatory Affairs
Dr. Luigi, Baroni	Director of Scientific Affairs
Dr. Giorgio Calderari	Chief Manufacturing Officer
Dr. Claudio Berettera	Project Leader
Dr. Alberto Macciocchi	Deputy Director, Clinical Affairs
Dr. Sergio Cantoreggi	Manager, Preclinical Development
Dr. Simona Parisi	Manager, Product Development

Consultants

[

Dr. Craig Lehmann Regulatory Consultant

Background:

IND for Palonosetron HCL Injection was submitted June 2, 1992 for prevention of cancer chemotherapy-induced nausea and vomiting. An End-of-Phase 2 Meeting between Helsinn and the Division was held March 10, 1999 and a follow-up teleconference to discuss clinical and biopharmaceutics issues was held April 29, 1999. A series of Special Clinical Protocol Assessment Requests were submitted by Helsinn beginning November 24, 1999 to discuss various aspects of the protocols for the proposed pivotal phase 3 trials. Chemistry, manufacturing, and controls (CMC) issues were discussed at a January 30, 2001 meeting to follow-up on the discussion at the End-of-Phase 2 meeting. A teleconference to discuss statistical issues was held October 18, 2001.

Helsinn has proposed an indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy. Three pivotal phase 3 studies were performed in support of the safety and efficacy of palonosetron: PALO-99-03 and PALO-99-04 for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy; and PALO-99-05 for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. In addition, the sponsor considers a phase 2, dose-ranging study (Study 2330) conducted by a prior sponsor, Syntex, supportive for the highly emetogenic claim.

The background package for this meeting was submitted to IND March 13, 2002 and included a long list of questions. To facilitate interaction with the firm, the Division's responses were faxed to Helsinn on Monday, April 8, 2002. Helsinn provided comments and requests in response to some of the Division's responses in a fax dated April 9, 2002. (The fax was submitted to IND April 17, 2002.) Helsinn's comments will be summarized below where appropriate.

Discussion Points:

1. After introductions, Helsinn presented a summary of the pivotal efficacy data from studies PALO-99-03, PALO-99-04, and PALO-99-05. The slides from this presentation were submitted to IND April 16, 2002.

2. The discussion turned to Helsinn's questions in the background package. The questions are italicized below, followed by the Division's response in bold. If discussion followed the question, a summary is placed in parenthesis after the Division's response.

Submission Format and Schedule

Specific Question #1: *NDA submission route and format. The palonosetron submission is planned to be a 505b1 NDA submitted in non-CTD (non Common Technical Document) format. The Division previously indicated that a non-CTD format is acceptable. Please confirm the acceptability of the planned non-CTD format for this NDA.*

Yes, this is acceptable.

Specific Question #2: *NDA submission schedule. The NDA is planned for submission in early September 2002. Please comment regarding any FDA-related factors that may affect the suitability of this planned submission schedule (do you foresee any problems with this submission schedule?).*

Yes, this is acceptable.

Clinical Questions

Specific Question #3: *Preliminary pivotal efficacy data. Given the preliminary phase 3 pivotal efficacy data submitted for PALO-99-03 and PALO-99-04 (see Appendix #1) and the preliminary PALO-99-05 efficacy data submitted not later than April 3, 2002, and assuming adequate safety data, we believe these efficacy data are sufficient to warrant submission of the NDA for the target indication. Please advise us if you agree and comment as needed.*

The adequacy of the efficacy data is a review issue. The clinical trial design for the prevention of acute (first 24 hours) chemotherapy induced nausea and vomiting (CINV) is adequate. The adequacy of the studies for the prevention of delayed CINV is a review issue.

[redacted]

Specific Question #4: *Noninferiority and possibly superiority. Primary and secondary efficacy data for both moderately emetogenic pivotal efficacy trials PALO-99-03 and PALO-99-04 (see Appendix #1) consistently indicate that 0.25 mg and 0.75 mg IV palonosetron doses are both noninferior to active comparators ondansetron 32 mg IV in PALO-99-03 and dolasetron 100 mg IV in PALO-99-04. Both palonosetron doses and active comparators clearly demonstrate greater efficacy than historical placebo in both studies, and active*

comparator results in both studies are similar to active comparator historical efficacy confirming assay sensitivity (trial validation). On day one, the 0.25 mg palonosetron group in PALO-99-03 demonstrated greater frequency of complete response than ondansetron 32 mg ($p < 0.025$), and the 0.25 mg palonosetron group in PALO-99-04 demonstrated greater complete response than dolasetron 100 mg IV ($p < 0.05$). Pending availability of preliminary efficacy data from PALO-99-05 (which is planned for submission to FDA well before the pre-NDA meeting, not later than April 3, 2002), if PALO-99-05 primary efficacy data also demonstrate superiority of palonosetron 0.25mg IV to ondansetron 32mg IV in highly emetogenic CINV, and assuming safety profiles are reasonably comparable, we plan to submit an efficacy superiority labeling claim for palonosetron 0.25 mg IV versus ondansetron 32 mg IV. We think this is consistent with labeling requirements in 21 CFR 201.57(c)(3)(v) and 314.126(b). Please comment regarding the feasibility of this approach.

If there is clear, independently substantiated evidence of superiority to other agents, such information may be included in the labeling, provided the comparison is to an appropriate regimen of the other agent. See ICH E10 for some guidance on this issue.

Specific Question #5: Prolonged efficacy of palonosetron. PALO-99-03 and PALO-99-04 efficacy data (at Appendix #1) for both palonosetron doses, particularly the 0.25 mg IV dose, consistently indicate statistically significantly greater efficacy days 2-5 post chemotherapy compared to the active comparator. Pending availability of PALO-99-05 efficacy data, please comment regarding the acceptability of including prevention of delayed nausea and vomiting within the proposed indication.

This is a review issue.

Specific Question #6a: ISE outline and plan. Please review the general organizational plan to preparing the ISE as described in section 4 of this background package, the ISE outline in the NDA Table of Contents (at item #9 of this background package) and the proposed selected ISE table shells at Appendix #2 and advise us if the proposed content and organization of the ISE is acceptable, advise us of changes you wish, and comment as needed.

The Table shells in Appendix #2 appear acceptable with the following additions to Table 9.6 2b-g on page 79: add the number of chemotherapy naïve and non-naïve patients; add the number of emetic episodes for all subjects; add the time to first

episode for all subjects; add the proportion of patients receiving cisplatin and the doses received; add type of malignancy; and add the time to first episode by gender. Add a Table after Table 9.6 2b-g to describe the disposition of patients, including, discontinuations from the trial and reasons for discontinuation.

Specific Question #6b: ISE, presentation of individual study efficacy data and pooled efficacy data. The principle presentation in the ISE will focus on individual trial presentation of the primary and selected secondary endpoints from the three pivotal trials (PALO-99-03, PALO-99-04 and PALO-99-05) and one supportive trial PALO-00-01 (which is the Syntex phase 2 study 2330 converted to a fixed-dose analysis versus historical placebo). Endpoints will be presented side by side, for each patient population (moderately and highly emetogenic). In addition, a pooled analysis for trials PALO-99-03, PALO-99-04 and PALO-99-05 will be performed. In this analysis an overall pooled analysis (all three studies) is planned first followed by pooled analysis stratified by emetogenicity (moderately separate from highly emetogenic CINV). The pooled efficacy analysis from the three pivotal studies will be considered supportive. Is this acceptable to FDA? Please comment.

This appears acceptable.

Specific Question #6c: ISE, presentation of repeat-dose efficacy data. Efficacy data for repeated doses of palonosetron will be presented using data from open-label study PALO-99-06. Initial cycle 0.25 mg and 0.75 mg single dose efficacy data from phase 3 pivotal studies PALO-99-03, PALO-99-04 and PALO-99-05 will be pooled with repeat-cycle efficacy data from PALO-99-06 (which involved only 0.75 mg doses) to analyze repeat-cycle efficacy for those subjects who received one or more repeat doses of palonosetron when they rolled-over from the phase 3 single dose studies to the open-label repeat-cycle PALO-99-06 extension trial. Is this approach acceptable to FDA? Please comment.

This appears acceptable.

Specific Question #6d: ISE, subgroup analysis. The following subgroup efficacy analyses will be performed on the pooled ISE database: gender; age (18-64, ≥ 65 years); age and gender; race (caucasian, black, Hispanic, other); regional differences (US/Canada, Europe, Mexico, Russia); chemotherapy status (naive vs non-naive); and concomitant medication usage (corticosteroids). These analyses will only be performed for the pivotal trial phase 3 pooled database (PALO-99-03, PALO-99-04 and PALO-99-05). Supporting efficacy study PALO-00-01 (which is the Syntex phase 2 study 2330 converted to a fixed-dose analysis versus historical placebo) is not planned for inclusion in this phase 3 study pooled database. Is this approach acceptable? Please comment.

These analyses should be performed on the individual trials as well as on the pooled data.

Specific Question #7a: ISS outline. Please review the proposed general organizational plan to preparing the ISS as described in section 4 of this background package, the ISS

outline in the NDA Table of Contents (section #9 of this background package) and the proposed selected ISS table shells at Appendix #3 and advise us if the proposed content and organization of the ISS is acceptable, identify changes you wish, and comment as needed.

This appears acceptable. A demonstration of the safety for each individual trial is still required in addition to the integrated data.

(NOTE: Helsinn stated that they plan to address individual study safety data in Sections 8.4 – 8.6 of the NDA rather than in the ISS. The Division responded that this approach appears acceptable.)

Specific Question #7b: SAE narratives. Individual narratives for serious adverse events (SAEs) reported in the palonosetron development program will be included in the ISS as an appendix. No narratives are planned for non-SAE events. Narratives will be organized by body system and indexed by body system and patient number. Is this plan acceptable? Please comment.

This appears acceptable.

Specific Question #7c: *Present AEs with frequency = 1%. In the ISS, events occurring at a level greater than or equal to 1% observed in the development program will be displayed in the in-text tables, with complete tables provided in the ISS supporting documentation. After providing an overall description of adverse events, the Sponsor will focus on selected treatment-emergent cardiac and vascular events. These selected events are preliminarily defined as: tachycardia, bradycardia, abnormal ECGs, chest pain, hypotension and hypertension, based on communication with the Agency (FDA letter dated August 3, 2001). The selected events will be analyzed further to ascertain whether subgroups of patients (elderly, renal impairment, cardiac impairment) are at greater risk compared to the general study population. Is this plan acceptable? Please comment.*

This appears acceptable.

Specific Question #7d: ECG data. The ISS will focus particular attention on results of ECG and Holter analysis. In addition, population PK/PD data will be provided evaluating the effect of plasma concentration on ECG findings (QTc and heart rate). For the ECG data, parameters will be presented for change from baseline to 15 minutes and change from baseline to worst value for all ECG parameters. Data will be presented for each subgroup of the integrated database outlined in Question #10 above, and further by sub-populations (gender, race, age, emetogenicity, doxorubicin 12-month cumulative dose, history of cardiac, renal or hepatic impairment) where appropriate. Is this plan acceptable? Please comment.

This appears acceptable.

Specific Question #7e: Holter data. As requested by FDA, phase 3 investigators rigorously recruited cancer patients to obtain Holter data. Holter data, collected only in the phase 3 pivotal trials in approximately 165 palonosetron patients and 50 active comparator patients, will be presented by treatment group, stratified by gender, age and the cardiac impairment subpopulation if appropriate. Is this plan acceptable? Please comment.

This appears acceptable.

Specific Question #7f: Additional subgroup analyses. The following safety subgroup analyses will be conducted in addition to standard demographic analyses: commonly used concomitant medications, concomitant illnesses including cardiac impairment, renal impairment and hepatic impairment to the extent possible. These analyses will only be conducted in the large phase 3 pooled database rather than on data from phase 1 and 2 since this population best reflects the target population. Is this plan acceptable? Please comment.

This appears acceptable.

Specific Question #7g: Repeat-cycle safety data. The safety database for repeated cycle palonosetron will be presented separately in the ISS from the single dose safety database. Is this acceptable to the FDA? Please comment.

This appears acceptable.

Specific Question #7h: One disqualified investigator from phase 2. One investigator from the overall Palonosetron clinical program has been disqualified by FDA. This investigator participated only in Syntex phase 2 trial 2330. We plan to exclude patients from this site from the ISE. Please advise us if you agree.

It is acceptable to exclude the results from this site from the efficacy analysis. The safety data from this site must be reported, however.

Specific Question #8a.

Redacted 1

pages of trade secret and/or confidential commercial information

Specific Question #9. Review of Clinical Section 8 of the proposed NDA table of contents. Please review overall Section 8 of the detailed proposed NDA table of contents (index) which is at section 8 of this background package. Please advise us of its acceptability and comment as needed.

It appears acceptable.

Specific Question #10. Request to use Patient Data Listings instead of Case Report Tabulations (CRTs) in the NDA. Patient Data Listings are included in appendices to all the palonosetron phase 2 and phase 3 trials. Patient Data Listings are organized by data category (i.e., all physical exam data for all patients are cited together with each patient's data identified, all SGOT values for all patients are cited together with each patient's data identified, etc), whereas, CRTs are organized by study by patient and include all study data for each patient listed by patient (this requires a lot of programming). We propose to (1) submit Patient Data Listings by study instead of CRTs, and (2) to submit Patient Data Listings only for phase 2 and phase 3 trials, all in hard copy. Please advise us if this is acceptable, and comment as needed.

We prefer CRTs. Patient Data Listings may be submitted in addition.

(NOTE: Helsinn proposed to prepare CRTs for phase 3 trials only and submit them in hard copy to the NDA. The Division responded that this is acceptable.)

Specific Question #11: Request to not duplicate PK reports for section 8 of the NDA. Helsinn intends to submit full PK reports for Section 6. However, we propose to not duplicate these reports for Section 8; instead, abstracts of these reports will be provided in Section 8.3 (clinical pharmacology). Is this acceptable?

Your proposal is acceptable.

Specific questions regarding the pharm/tox program

Specific Question #12: Rat carcinogenicity data. Based on the data available to date and on the considerations preliminarily presented in the cover letter of IND Amendment #130, we think the positive findings in the rat carcinogenicity assay are unlikely to represent a significant risk to patients receiving palonosetron. Accordingly, we plan to describe these carcinogenicity study results in proposed draft labeling. Please share with us your thoughts about this approach and comment as needed.

This is a review issue.

(NOTE: In response to Helsinn's question, the Division explained that it is unlikely that comments and recommendations regarding the carcinogenicity studies will be provided prior to NDA submission.)

Specific Question #13: *Overall Pharm/Tox Program. The pharmacological and toxicological profile of palonosetron has been thoroughly characterized. The results of all studies outlined in Appendix #5 of this package constitute, in our opinion, a complete pre-clinical program. Please advise us if you agree and provide comments as needed.*

Your program appears to be complete, but this is a review issue.

Specific questions regarding the CMC program–brief summary of remaining issues or new data since FDA meeting Jan 02, status of DMF/HAS DS. (5 min)

Specific Question # 14: [redacted]

This appears acceptable.

Specific Question # 15: *Specifications for Drug Substance and Drug Product. Specifications for the drug substance and drug product have been revised based on Agency comments during the January 30, 2001 meeting and review of available release and stability data. Revised specifications are provided in the summary background package, section 6. Please confirm that the revised specs are acceptable.*

We suggest lowering the Total Impurities specification to less than [redacted] based on the actual batch test data.

(NOTE: The Division explained that, if the data justify a Total Impurities specification less than [redacted], the specification should be lowered. The acceptability of the revised specifications is a review issue. The transfer of drug product manufacture from [redacted] to [redacted] should be clearly documented.)

Specific Question # 16: *Drug Product Stability. As discussed at the January 30, 2001 meeting, drug product stability data from [redacted] batches will be included in the NDA in support of the expiration date. Up to [redacted] months data are available on [redacted] batches and up to [redacted] months supportive data are available on [redacted] batches. Batches*

manufactured by — and —— were well within the limits for finished drug product stability as proposed in the NDA specifications.

As discussed at the meeting and noted in the minutes, an update to the stability data for — —— manufactured batches is planned during the review period. One additional data set representing the — month test station at —— will be provided during the NDA review cycle. Please confirm that this approach is still acceptable.

Expiration dating of the drug product should be based on the primary stability data from the commercial manufacturing site, —— Additionally, it is expected that adequate stability data will be presented for evaluation from the proposed commercial drug substance manufacturing site [Helsinn Advanced Synthesis (HAS)] for comparison with the previous manufacturers; — Stability data generated from sites other than the proposed commercial manufacturing sites are considered to be supportive. Clarify the amount of site specific stability data that will be available or submitted in the NDA and the submission time line for that data.

[NOTE: (Please refer to the submission to IND [redacted] dated April 17, 2002 for the complete text of Helsinn's response.) Helsinn explained that they would submit — months of drug substance stability data on drug substance manufactured by Helsinn Advanced Synthesis. Stability data for drug substance manufactured by is not available. They plan to submit the following drug product stability data: —months of data from 1 batch of — mg/mL and 2 batches of — mg/mL manufactured by —— (Drug substance manufacturer is . nonths of data from 3 batches of both strengths manufactured by —— (HAS is the drug substance manufacturer). The Division emphasized that the complete stability data set should be submitted in the NDA or a DMF. Data from —— will be the primary stability data and — data will be supportive. The Division commented that the proposed plan appears acceptable.]

Specific Question # 17: *Review of CMC Section 4 of the Proposed NDA Table of Contents. Please review Section 4 of the proposed detailed NDA Table of Contents which is located at Section 9 of this background package. Please advise us of its acceptability.*

This appears acceptable.

Specific questions regarding the Biopharm program

Specific Question #18: *Request for waiver of in-vivo bioavailability study for palonosetron NDA drug product. Helsinn plans to request a waiver of the requirement in 21 CFR 320.21 to submit evidence demonstrating the in vivo bioavailability for Palonosetron HCl Injection drug product on the basis that the bioavailability of this I.V. dosage form is self-evident as stated in 21 CFR 320.22. The request for waiver will be placed in Section 6 of the NDA*

where a traditional bioequivalence section would normally reside. Is this overall plan acceptable?

A waiver is not required for I.V. products.

Specific Question #19: Do we need a request for waiver of in-vivo bioequivalence study to demonstrate the bioequivalence of the phase 2 and phase 3 formulations of IV palonosetron. Phase 2 studies were performed using a somewhat different formulation of IV palonosetron than was used in phase 3 studies. The phase 3 formulation is the NDA formulation. The phase 2 formulation [redacted] *IV administration. The phase 3 formulation is a 5 ml aqueous vial ready for IV injection. Both phase 2 and phase 3 palonosetron drug products were administered by IV bolus over 30 seconds. Please advise us if we need to request a waiver in the NDA for demonstrating the bioequivalence of the phase 2 and phase 3 IV formulations. If needed, the proposed basis for the request for waiver is that the bioequivalence of these two IV dosage forms is self-evident. If the request for waiver is required, please advise us if this proposed basis for the waiver is acceptable, and please advise us if placing the request for waiver in Section 6 of the NDA where a traditional bioequivalence section would normally reside is acceptable.*

The waiver request should be placed in the formulation discussion.

Specific Question #20: Review of Clinical Section 6 of the proposed NDA table of contents. Please review section 6, the "Human Pharmacokinetics & Bioavailability" section of the detailed proposed NDA table of contents (index) which is at section 9 of this background package. Please advise us of its acceptability and comment as needed.

Include a discussion of the pharmacokinetic/pharmacodynamic aspects of QT prolongation and a discussion of drug-drug interactions.

Specific Questions regarding the outline of Proposed Draft Labeling

Specific Question #21: Acceptability of proposed draft labeling outline. Please review the proposed draft labeling outline in section 8 of this background package. Presently there are no data in the outline. Please advise us if the proposed outline is acceptable and comment as needed.

The outline appears acceptable. We have concerns, however, about the mock-up tables. We will elaborate on our concerns at the meeting.

(NOTE: The Division explained that any comparison in the labeling to other active drugs must be carefully evaluated and substantiated. The inclusion of a p-value for palonosetron versus a historical placebo control is unlikely to be acceptable for inclusion in the labeling. While this comparison may be used to draw conclusions about efficacy, it is not scientifically valid enough for inclusion in the labeling. It is generally more favorable to include confidence intervals rather than p-values. It may be preferable to refer to ondansetron or dolasetron as "the active comparator" rather than to specifically name them.)

Specific Question #22: *Adverse Events section of labeling. The proposed AE tables in the Adverse Events section of labeling proposes to present AEs occurring in = 2% of adult patients in chemotherapy-induced nausea and vomiting clinical studies. Please advise us if the 2% cutoff is acceptable.*

This is acceptable.

Specific Question #23: *Request to exclude certain sections of labeling. Helsinn requests to exclude the following sections to labeling since these sections are not applicable to the use of IV palonosetron in the target patient population or are often excluded from labeling: Information for Patients, and the Medication Guide required under 21 CFR 208, Labor and Delivery,*
Substance, Abuse, Dependence, *Animal Pharmacology and/or Animal Toxicity, and Clinical Studies and References (we anticipate no references to the published literature). Please advise us if exclusion of these labeling sections is acceptable.*

The Medication Guide; Information for Patients; Controlled Substance, Abuse, Dependence; Animal Pharmacology and/or Animal Toxicity; and References sections may be omitted. The remaining sections must be included, with a notation, where appropriate, that no data are available.

Regulatory discussion items

Specific Question #24: *Acceptability of overall proposed detailed NDA table of contents. Please review the overall format and content proposed for the detailed NDA Table of Contents in section 9 of this background package, advise us of its acceptability and comment as needed.*

This is acceptable. The Table of Contents must be specific enough to easily locate items.

Specific Question #25: *Electronic databases to be submitted in conjunction with the NDA. We plan on submitting the following electronic databases in conjunction with the NDA: draft labeling, NDA Summary excluding the CMC summary subsection, ISS database, ISE*

database, carcinogenicity databases, and CRTs (Patient Data Listings). Please advise us if this list is acceptable and comment. Please advise us whether we should submit these electronic databases in the initial NDA filing or within 30 days or so after NDA submission.

Please submit the electronic databases when the NDA is submitted. Clarify if the entire NDA will be submitted electronically or only subsections. Please consult the following Guidances for Industry regarding electronic submissions: (1) "Regulatory Submissions in Electronic Format, General Considerations" (January, 1999); and (2) "Regulatory Submissions in Electronic Format, New Drug Applications" (January 1999). Please clarify if any CMC data will be submitted electronically.

(NOTE: Helsinn explained that they plan to submit the entire NDA in hard copy and supplement with electronic versions of the summary volume, draft labeling, ISS and ISE data files, and carcinogenicity data files. The Division responded that stability data should be submitted in SAS Transport Version 5. It was noted that WORD 97 is used for word processing.)

Specific Question #26: RTF checklist. In addition to the information listed in 21 CFR 314.101, please provide us with the refuse-to-file checklist that the Division uses for determining whether an application may be filed.

No RTF checklist exists.

Specific Question #27: Financial Certification, Form FDA 3454. Key clinical efficacy studies performed for the NDA include pivotal studies PALO-99-03, PALO-99-04 and PALO-99-05 which Helsinn sponsored during the last 2 years, plus supporting efficacy study 2330 which was sponsored and performed previously by Syntex (now Roche) in the early 1990s. Form 3454 (at Appendix #5) has three checkboxes for certification and directs the sponsor to "certify to one" of the boxes. Helsinn can certify to box (1) for PALO-99-03, PALO-99-04 and PALO-99-05 which Helsinn sponsored, but it appears based on tentative feedback from Roche (Syntex) that Helsinn may also need to certify to box (3) for Syntex sponsored study 2330 which Helsinn acquired from Roche. Please advise us whether (1) we should certify to both boxes (1) and (3) on the form, or whether we should submit a separate form for study 2330, or how else we should accomplish this certification. Also, since establishing efficacy in the NDA will be based on PALO-99-03, PALO-99-04 and PALO-99-05 and also 2330 as described above, please confirm that these are the only studies for which we will need to provide financial certification by the Helsinn (the applicant) in the NDA.

Please submit separate Forms FDA 3454 for the studies sponsored by Helsinn (PALO-99-03, PALO-99-04, and PALO-99-05) and the study sponsored by Syntex (Study 2330) and check the appropriate box on each form. Clearly indicate to which study(s) the form is applicable. If you check box three, you must attach detailed information

describing your attempts to obtain the information required under 21 CFR 54.4 and why this information could not be obtained.

Specific Question #28: FDA review of proprietary name for palonosetron. Helsinn plans to submit 2-5 proposed proprietary names to the IND within the next few months with NDA submission planned for early September 2002. We understand there is a backlog at OPDRA for review of proprietary names. Please advise us of the estimated amount of time required for FDA/OPDRA to review the candidate names and advise us of a preliminarily acceptable proprietary name.

It is estimated that a review of proposed tradenames for an application in the IND stage will take 90 to 120 days and only two names may be reviewed at a time. Please submit the proposed tradename(s) to your IND and include the proposed dosage regimen, indications, and adverse event profile.

Specific Question #29: Readiness of the overall palonosetron program for NDA submission. Given the information presented in this pre-NDA background package, interactions with FDA to date, and the preliminary PALO-99-05 efficacy data, which we plan to submit to FDA not later than April 3, 2002, we believe the Palonosetron development program will be ready for NDA submission in early September 2002. Please advise us if you agree.

The NDA appears to be ready for submission. Filing decisions are based on an initial review of the actual submission.

DECISIONS (AGREEMENTS) REACHED:

None.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None.

Minutes Preparer:

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.

Chair Concurrence:

{See appended electronic signature page}

Hugo Gallo-Torres, M.D., Ph.D.

Drafted by: BKS/April 17, 2002
R/d init: JC/April 19, 2002
TP/April 18, 2002
EPD/April 18, 2002
HGT/April 25, 2002
Finaled: BKS/April 30, 2002
Filename: Palonosetron Minutes.doc

MEETING MINUTES

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

/s/

Hugo Gallo Torres
4/30/02 05:14:41 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 30, 2001
Time: 9:00-10:30 A.M.
Location: Conference Room M (PKLN)

Application: IND [redacted] Palonosetron Injection

Type of Meeting: Discussion of Chemistry Issues

Meeting Chair: Dr. Liang Zhou, Chemistry Team Leader

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Liang Zhou, Chemistry Team Leader
Dr. Joe Sieczkowski, Chemistry Reviewer
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of New Drug Chemistry II (HFD-820)
Dr. Steve Koepke, Deputy Director

External Constituent Attendees and titles:
Helsinn Healthcare SA
Dr. Giorgio Calderari, Director, Corporate Technical Affairs
Dr. Dario Ceriani, Senior Manager, Regulatory Affairs, Helsinn
Dr. Waldo Mossi, Manager, Scientific Division, Helsinn

Dr. Craig Lehmann, Regulatory Consultant and Authorized Representative for the IND
Mr. Franco DeVecchi Sr., Authorized US Corporate Representative

Background: IND [redacted] was submitted by Syntex Laboratories, Inc. on June 2, 1992 to investigate RS-25259-197 (now referred to as palonosetron) Injection, a 5-HT_3 antagonist, in the treatment of cancer chemotherapy-induced nausea and emesis. The IND was subsequently transferred to Helsinn
Healthcare SA.

An End of Phase 2 meeting was held between the FDA and the sponsor on March 10, 1999 (minutes available).

In a November 22, 2000 submission to the IND, the sponsor's representative requested a meeting with the Division to discuss the production of drug product registration batches and initiation of the drug product stability program for those batches.

Meeting Objectives:

1. To discuss the production of drug product registration batches

2. To discuss the initiation of the drug product stability program for the drug product registration batches

Discussion Points: The firm's January 16, 2001 pre-meeting submission contained several specific questions and "salient points" for the Division to address. The firm's questions and salient points are reproduced below in regular type; the Division's responses are in bold type.

SPECIFIC QUESTIONS:

1. Does the Division agree to the continued use of development and Phase 3 clinical batches of drug product manufactured by ——— representing the 2 strengths, — mg/mL and — mg/mL, as primary stability data (up to — months) to support the expiration date?

   Agency Response: This proposal is acceptable, provided there are no other significant changes. We consider specific comments on the expiry period to be premature at this time.

2. Does the Division agree to the manufacture of three registration batches of drug product manufactured by ——— with up to —months data at the time of NDA submission?

   Agency Response: In general, ICH Q1A recommends 12 months of primary stability data. However, your proposal is acceptable, based on the supporting data and other changes made in the drug product.

3. Does the Division agree to the addition of drug product stability data to the NDA registration batches during the NDA review period? If the CMC section of the NDA is pre-submitted, an update to the NDA registration batches stability data will be necessary.

   Agency Response: Please refer to our response to question 2. Note that if you submit a presubmission, the entire chemistry, manufacturing, and controls (CMC) section (as defined in 21 CFR 314.50) must be complete (including all manufacturing facilities being ready for inspection) at the time of submission.

4. Does the Division agree that submission of additional data will be accepted as a Minor Amendment to the NDA, thereby not restarting the NDA review time?

   Agency Response: The decision as to whether an amendment will be classified as major or minor will depend on the data it contains.

SALIENT POINTS FROM THE PRE-MEETING DOCUMENT

Drug Substance:

5. The manufacturing site for the drug substance has been changed from [redacted] to Helsinn Advanced Synthesis (HAS). Phase 3 clinical studies are planned to continue using existing drug product manufactured using drug substance from the [redacted] site as described in IND Amendment #74, Volume 2, page 001, dated April 7, 2000.

   Comment: This plan is acceptable. Please see our comment on point six, below, and ICH Q3A, Q3C, and Q6A guidelines.

6. As discussed at the End-of-Phase 2 Meeting, it was agreed that as a consequence of the technology transfer activities and results, the drug substance manufactured by HAS would be submitted in the NDA without having been exposed to clinical trials.

   Comment: This plan seems reasonable, however, note that we have limited information re: impurities and analytical test methods.

7. Comparative data for drug substance manufactured at both sites indicate equivalence in physical and chemical properties. No differences in the quality or properties of the drug substance have been seen in drug substance manufactured by both manufacturing facilities. A change in the source of the starting material used in [redacted] of the drug substance synthesis was implemented during the site transfer. No significant changes in the manufacturing scheme or equipment have occurred in the site transfer. The synthesis route used by both manufacturing facilities is the same.

   Comment: This information is noted.

8. Reference is made to IND amendment Serial #89 dated 8 September, 2000, for information regarding the new [redacted] methods and updated analytical specifications. New [redacted] methodology has been submitted that is capable of quantitating palonosetron HCl, impurities in palonosetron HCl drug substance, and detection of possible diastereoisomers and enantiomers of palonosetron HCl.

   Comment: Please see our response to point six, above. Also, provide comparative test data to justify the proposed [redacted] method. Appropriate specifications should be established.

9. The drug substance stability strategy is based on 12 months long-term ([redacted]) and 6 months accelerated data on drug substance manufactured at HAS. These data will be available at the time of NDA filing as commercial site-specific data.

   Comment: This proposal appears adequate. Generally, drug substance stability protocols provide for re-test periods to ascertain acceptability of the drug substance at release.

Drug Product:

10. — is being introduced as the site of manufacture for commercial drug product. The manufacturer for Phase 3 drug product is — Due to the closure of the — manufacturing facility in June 2000, — was selected as the manufacturer of commercial drug product. No significant changes in the manufacturing process or equipment will occur with the site transfer. The formulation and container closure system were not changed.

Comment: This information is noted.

11. As discussed with FDA during the End-of-Phase 2 Meeting, three site-specific NDA registration batches (of each formulation) will be manufactured. The site-specific NDA registration batches will be manufactured by — and will contain 3 registration/validation lots of drug substance manufactured by HAS. — months stability data (of a — months program) from the development and Phase 3 batches manufactured by — representing the 2 strengths of drug product will be presented as primary stability data. Up to — months stability data from the commercial batches manufactured by — will be presented as supportive stability data. The stability strategy is based on stability studies of the two strengths of Palonosetron HCl Intravenous Injection proposed for commercial market and submission of long-term supportive data, however only one concentration will be submitted in the NDA depending upon the clinical trials results.

Comment: This information is noted.

12. A maximum batch size of — is being proposed for commercial product. The commercial batch size will likely be — The batch sizes of the NDA registration/stability batches will be up to — The batch size of the registration/stability batches will not be impacted by the commercial batch size, as the product is a solution and solubility of the drug substance is not an issue. Furthermore, the product is — sterilized and — including parameters and performance specifications, for both the stability and commercial batches will be identical. The size of the — will be different, as the stability batch size is smaller than the commercial batch size. The — for the NDA registration batches will have no impact on the chemical stability of the drug product. The — will be validated for the — and the commercial batch size will be fully validated.

Comment: If there are specific Microbiology concerns, these should be raised. Alternatively, you can submit these concerns, and we will consult them to Microbiology for review and comment.

13. As previously stated (see item #8 above), reference is made to IND amendment Serial #89, dated 8 September 2000, for information regarding the new — methods. Two new — methods have been submitted to the IND (Serial #89) that are capable of quantitating palonosetron HCl and impurities in the drug product. Method — employing — technology, will be used to quantitate the specified and known potential impurities and Method — will be used to detect and quantitate unknown impurities and the potency of palonosetron HCl in the drug product.

    Comment: Improvement in — test methods are always appreciated. However, questions related to test data and methods are review concerns.

14. Stability data on registration/stability lots will be generated with the new — methods.

    Comment: This plan is acceptable.

In addition, the Division conveyed the following general comments:

1. **The drug substance and drug product specifications should be tightened significantly. There should also be specifications for specified impurities.**

2. **Specifications should be based on the ICH proposed impurity limits.**

3. **Please ensure that you have a proposed tradename and USAN name.**

/s/

Melodi McNeil
2/27/01 02:06:08 PM

Meeting Minutes File

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 29, 1999
Time: 9:30-11 AM
Location: Room 6B-45 (PKLN)

Application: IND [redacted] Palonosetron Injection

Type of Meeting: Follow-up to March 10, 1999 End of Phase II meeting (via teleconference)

Meeting Chair: Dr. Lilia Talarico, Division Director

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Ms. Melodi McNeil, Regulatory Health Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (HFD-870)
Dr. David Lee, Biopharmaceutics Team Leader

External Constituent Attendees and titles:

Helsinn Healthcare SA
Dr. Luigi Baroni, Director, Business Development
Dr. Claudio Berettera, Manager, Licensing In-Project Leader
Dr. Dario Ceriani, Senior Manager, Regulatory Affairs
Dr. Alberto Macciocchi, Senior Manager, Product Development

Consultants
Dr. Craig Lehmann, August Consulting, Principal Consultant

Background: IND [redacted] was submitted by Syntex Laboratories, Inc. on June 2, 1992 to investigate RS-25259-197 (now referred to as palonosetron) Injection, a 5-HT_3 antagonist, in the treatment of cancer chemotherapy-induced nausea and emesis. The IND was subsequently transferred to Helsinn Healthcare SA.

An End of Phase II meeting was held with the sponsor on March 10, 1999 (minutes available). Although there were biopharmaceutics items on the meeting agenda, the Division's clinical

pharmacology representative was unable to attend, due to illness. The sponsor requested and was granted a follow-up teleconference to discuss the biopharmaceutics issues that were originally scheduled to be discussed at the March 1999 End of Phase II meeting.

Meeting Objective: To discuss the biopharmaceutics issues that were originally scheduled to be presented at the March 1999 End of Phase II meeting

Discussion Points (bullet format): In the February 15, 1999 briefing package the firm requested the Agency's response to (among others) the following question:

1. Please provide feedback regarding the acceptability of the overall proposed biopharmaceutics program to support an NDA for palonosetron HCl.

The Agency had the following comments (printed below in bold type):

a. Overall, the proposed biopharmaceutics program appears acceptable; the proposed Phase III fixed dose seems to be justified.

b. We note that Phase I data were collected largely in males. It is unclear whether these data apply to females.

The sponsor summarized the data that have been collected to date and acknowledged that there is insufficient information to characterize any gender differences in the palonosetron pharmacokinetics. The firm indicated they plan to collect population pharmacokinetic data in the planned Phase III clinical trials, and this approach was acceptable to the Division. The Division commented that the ultimate acceptability of the study would depend on the appropriateness of the protocol design and the data.

c. Regarding the protocol for the population pharmacokinetic study, please refer to the Guidance for Industry, entitled "Population Pharmacokinetics." We advise that this protocol be submitted for FDA review and comment prior to its execution.

d. We advise in vivo drug interaction studies, since in vitro studies are not always predictive. Consider assessment of any drugs likely to be co-administered with palonosetron.

e. [redacted]

f. Please evaluate whether palonosetron is metabolized into the potentially toxic impurity [redacted] or its derivatives.

The sponsor commented that, based on a radio-labeled ADME study, there is no evidence to suggest that palonosetron is metabolized to —— They added that results from this study apply to both genders and agreed to clearly provide this information in the NDA. They also agreed to characterize metabolite 4 (M4), an . RS-25259 which occurs as a result of CYP450 metabolism and appears in the urine.

g. **Consider a study of palonosetron in hepatically impaired subjects, since this compound is more than 50% metabolized and its therapeutic index is uncertain.**

It was agreed that to address this comment, the sponsor would 1) re-evaluate the data from the radio-labeled ADME study and 2) enroll hepatically impaired patients into the planned clinical trials, then evaluate them via population pharmacokinetics.

2. In response to a question from the Division, the sponsor reiterated that the drug product formulation planned for the Phase III clinical trials is identical to the formulation planned for marketing, although the products will employ drug substance from different sources. It is the firm's position that the Phase III program will appropriately characterize the pharmacokinetic parameters of the to-be-marketed formulation. The Division responded that the firm's plan is acceptable for now and agreed to inform the firm if this decision changes.

3. The sponsor requested additional discussion on two points in the March 10, 1999 meeting minutes (the Division's responses are in bold print):

   a. In the March 1999 meeting the sponsor was advised to conduct the planned Phase III clinical trials in chemo naïve patients, however, the sponsor prefers to enroll both naïve and non-naïve patients.

   It is acceptable for the sponsor to study both patient types, however, there should be sufficient numbers of patients in each group to allow a valid subset analysis. In response, the firm agreed to stratify according to this parameter.

   b. In the March 1999 meeting the sponsor was advised that the primary endpoint of the pivotal studies should be "complete response," defined as no emesis, no retching, no rescue medications, and -at the most- mild nausea. The sponsor prefers a primary endpoint of no emesis, no rescue and no retching.

   As currently planned, the phase III studies will use approved $5HT_3$-receptor antagonists (such ondansetron and dolasetron) as active comparators. After some discussion, it was agreed that the primary endpoint used in the pivotal studies for palonosetron should be identical to the primary endpoint used in the pivotal studies that supported approval of the active comparator. (The sponsor has

received the summary bases of approval for these products through the Freedom of Information Act; the design and endpoints for the pivotal studies are also described in each approved product's package insert).

Minutes Preparer: /S/ 5/12/99

Chair Concurrence: /S/ 5-12-99

cc: Original IND [redacted]
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/McNeil (2 copies)
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-870/Lee

Drafted by: mm/May 6, 1999/c:\mydocuments\cso\minutes\[redacted]t-con-min.doc
Initialed by: DLee 5/7/99
HGallo-Torres 5/11/99
LTalarico 5/11/99
final: May 12, 1999

MEETING MINUTES

Meeting Minutes
Files

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 10, 1999
Time: 1-3 PM
Location: Conference Room K (PKLN)

Application: IND [redacted] Palonosetron Injection

Type of Meeting: End of Phase II

Meeting Chair: Dr. Lilia Talarico, Division Director

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Lawrence Goldkind, Medical Officer
Dr. Jasti Choudary, Pharmacology Team Leader
Dr. Yash Chopra, Pharmacology Reviewer
Dr. Eric Duffy, Chemistry Team Leader
Ms. Kati Johnson, Supervisor, Project Management Staff
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of Biometrics (HFD-715)
Dr. Mohamed Al-Osh, Acting Statistical Team Leader

External Constituent Attendees and titles:

Helsinn Healthcare SA
Dr. Luigi Baroni, Director, Business Development
Dr. Claudio Berettera, Manager, Licensing In-Project Leader
Dr. Dario Ceriani, Senior Manager, Regulatory Affairs
Dr. Giorgio Calderari, Senior Manager, Corporate QA
Dr. Alberto Macciocchi, Senior Manager, Product Development

Consultants

Dr. Craig Lehmann, August Consulting, Principal Consultant

Background: IND was submitted by Syntex Laboratories, Inc. on June 2, 1992 to investigate RS-25259-197 (now referred to as palonosetron) Injection, a 5-HT_3 antagonist, in the treatment of cancer chemotherapy-induced nausea and emesis. The IND was subsequently transferred to Helsinn Healthcare SA.

In a December 23, 1998 submission the sponsor described plans to develop palonosetron hydrochloride injection for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV), including highly emetogenic chemotherapy such as cisplatin, summarized palonosetron's clinical development to date and requested an End of Phase II meeting to get the Division's input on 1) the planned phase III development program, 2) the adequacy of the technology transfer plan of drug substance from the — facility to the Helsinn Switzerland facility, and 3) the sufficiency of the preclinical study data to support a future NDA.

According to the firm, two Phase II clinical trials have been conducted to establish the safety and efficacy of intravenous palonosetron HCl in the prevention of highly emetogenic CINV. One study (**Study 2120**) was aborted after only two patient admissions, due to poor enrollment, therefore only **Study 2330** will be summarized here.

Study 2330 was a single-dose, double-blind, parallel, multi-center dose-ranging study in which 161 patients (129 males, 32 females) were randomized to 0.3, 1, 3, 10, 30, or 90 mcg/kg of palonosetron. According to the firm, the objective was to determine dose-response over a wide range of palonosetron doses, using the low-dose levels of palonosetron for control. The primary efficacy measure was the proportion of patients with no emetic episodes and no rescue medication. When compared to the lowest doses (0.3 and 1 mcg/kg) only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident.

Meeting Objectives:

1. To get the Division's input on the planned phase III development program,
2. To determine the adequacy of the technology transfer plan of drug substance from the — facility to the Helsinn Switzerland facility, and
3. To evaluate the sufficiency of the preclinical study data to support a future NDA.

Discussion Points: In the February 15, 1999 briefing package the firm requested the

Agency's response to the following questions (Note: The firm's questions are reproduced below in regular type; the Agency's responses are in bold type.):

Manufacturing – Question 1

Is the described Commercialization Development Plan sufficient?
If not, what additional steps are recommended?

- **The plan as described appears reasonable, however, specific steps needed will be dependent on data generated during the plan's execution.**

- **We note your plan to use drug substance manufactured by —— (date of manufacture: 1995) for your Phase III drug product. The age of that drug substance is a potential problem.**

  (Note: In response to this comment, the sponsor's representatives indicated that they plan to change the drug substance manufacturer prior to submission of an NDA; Helsinn-manufactured drug substance will be incorporated into the drug product planned for commercial use. The Division's chemistry representative indicated that the information to support this change should be presented clearly and completely in the NDA. He said the Helsinn drug substance manufacturing facility(ies) should be prepared to host an inspection at the time of NDA submission. He also said that three batches of drug product manufactured with Helsinn drug substance should be put on stability; at least one of those batches should be commercial scale.)

- **Please conduct degradation studies to ascertain whether the impurity —— is also a degradant. In addition, we advise that you conduct clinical ADME studies to see if this compound is a metabolite. Synthesize the metabolite of —— for use as a reference standard in the ADME studies.**

  (Note: In response to this comment, the sponsor's representatives indicated that under stress conditions, —— is a potential degradant.)

- **We note that the impurity specifications seem to be much higher than warranted; the specifications should be based on observed data and manufacturing capabilities.**

Pre-Clinical – Question 2

Per Amendment #58 to the IND, will the conduct of the 9 month dog toxicology study utilizing the oral route of administration in lieu of the IV route be acceptable?

- This proposal is not acceptable. Toxicology studies should employ the same route of administration as the route employed in the clinical studies. Because of the differences in the extent of metabolism and the consequent relative exposures to RS-25259-197 and its metabolites between the oral and i.v. routes, the proposed 9-month study in dogs and the 6-month study in rats should be conducted with i.v. administration of RS-25259-197.

- Given that —— was cardiotoxic to healthy male subjects in a previously conducted study, safety pharmacology studies should be undertaken with state of the art methods (See Carlsson et al., J. Pharmacol Exptl Therap 282:220-227, 1997) to characterize the potential effects of RS-25259-197 and its —— on cardiac electrophysiology. Such testing should assess the Class III effects and proarrhythmic properties. The tests should employ 1) in vivo anesthetized guinea pig and rabbit models, 2) in vitro voltage clamp studies in isolated ventricular myocytes, 3) in vitro studies in isolated cardiac tissues (guinea pig papillary muscle and canine and rabbit Purkinje fibers) for effects on action potentials, and 4) in vitro studies in isolated cells for specific effects on ionic channels. RS-25259-197 and —— should also be tested for their serotonin ($5HT_4$) agonistic and antagonistic activities in isolated guinea pig proximal colon.

- Protocols PALO-99-05 and PALO-99-06 propose the coadministration of palonosetron with dexamethasone, however, no toxicity data has been provided on the combination. Please conduct short-term toxicity studies on this combination (palonosetron and dexamethasone).

- **In vitro metabolic studies should be undertaken to determine the potential for interconversion of RS-25259-197 to [redacted].**

Pre-Clinical – Question 3

Are the doses for rat carcinogenicity (previously recommended by the FDA) acceptable?

- **The doses for the rat carcinogenicity study are acceptable.**

Pre-Clinical – Question 4

Is the rat carcinogenicity sufficient to address the potential for carcinogenicity?

- **Carcinogenicity potential needs to be assessed by testing in two species, therefore, the rat carcinogenicity study alone is not sufficient to address palonosetron's carcinogenic potential. A mouse carcinogenicity study (with previously FDA recommended doses) is needed as well, particularly since this compound is genotoxic.**

Clinical – Question 5

Are the two trials presented in moderate dose CINV, with repeat cycle and [redacted] considered sufficient to support the label claim "Prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy"?

- **This question is premature. The program appears adequate, however, all regulatory decisions, including any labeling claims, will be data driven. (Division representatives also noted that a dose response was not shown in Phase II Study 2330, and therefore it is questionable whether the appropriate palonosetron dose has been identified.)**

Clinical – Question 6

Is 2330 sufficient to support the label claim "Including high dose cisplatin"? Should a historical control analysis be conducted?

Note: In the question above, the firm appears to have written "high dose cisplatin" when "highly emetogenic chemotherapy" is what was intended. (In response to this comment, the firm indicated that more than 60% of patients in Study 2330 got a cisplatin dose of $\geq$ 80 mg/m^2 infused over three hours or less.)

- **Due to the lack of a dose response in this study, these data are inadequate to serve as pivotal efficacy support (although they may be useful as supportive data).**

(After discussion with the firm, it was agreed that the results of Study 2330 versus a historical control, along with another study in which two doses of palonosetron are compared to ondansetron, then validated by comparison to a historical control could be used to support a claim for palonosetron in the prevention of nausea and vomiting due to highly emetogenic chemotherapy. Note: Any regulatory decisions will be data driven.)

Clinical – Question 7

Are safety data from 2274 volunteers and patients including 1200-1700 repeat cycles included in the safety database sufficient to support labeling of palonosetron HCl?

- **This question is premature. The response will depend on the adverse event profile from the Phase III studies. (Note: The sponsor was advised to present adverse events from the clinical trials per cycle and per patient. The Division recommended that sufficient numbers of patients be enrolled so that rare adverse events can be assessed. Further, the drug should be assessed in a variety of subpopulations including patients with liver and kidney impairment, patients of both genders and all ages, patients with a predisposition to cardiovascular problems, and patients on concomitant drug therapy which may predispose them to cardiac arrhythmias. The number of patients assessed can be increased through open label studies.)**

- **For more information, consult the Guidance for Industry on Safety Evaluation.**

Clinical – Question 8

Can a description of a trial which evaluates the ——— with——— palonosetron HCl be included in the clinical trials section of the labeling?

- **This question is no longer relevant, as the firm no longer plans protocol-specified ——— and palonosetron. In general, however, the CLINICAL TRIALS section of the package insert will describe the clinical trials (as they were conducted) which provided pivotal support for the labeled indication.**

Clinical – Question 9

Please provide feedback regarding the acceptability of the overall proposed biopharmaceutics program to support an NDA for palonosetron HCl.

- **Overall, the proposed biopharmaceutics program appears acceptable; the proposed**

Phase III fixed dose seems justified.

- We note that Phase I data were collected largely in males. It is unclear whether these data apply to females.

- Regarding the protocol for the population PK study, please refer to the Guidance for Industry, entitled "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions." We advise that this protocol be submitted for FDA review and comment prior to its execution.

- We advise in vivo drug interaction studies, since in vitro studies are not always predictive. Consider assessment of drugs likely to be co-administered with palonosetron.

- [redacted]

- Please evaluate whether palonosetron is metabolized into the potentially toxic impurity [redacted] its derivatives.

Note: The Division's biopharmaceutics representative was unable to attend today's meeting due to illness. The firm indicated they would request a separate teleconference with the Division to follow up on these comments.

Clinical – Question 10

Specific feedback on the Phase 3 protocol outlines is requested.

- Note: The background package contained only protocol summaries, therefore the Division's comments are necessarily limited in scope. Also, at today's meeting the sponsor distributed a revised protocol PALO-99-05 (the protocol no longer provides for mandatory co-administration of palonosetron and [redacted]. Due to the short notice, division representatives were not able to review this revised protocol in detail.

- Regarding PALO-99-03 and PALO-99-04:

  1. Include patients on all chemo agents considered "moderately emetogenic" including those patients on doses of cisplatin less than or equal to 50 mg/m^2.

  2. The assessment of time to first emesis should include a prespecified subset analysis

by chemotherapeutic agent.

3. All secondary efficacy measures should be evaluated daily, not at the intervals proposed.

4. We recommend Holter monitoring 24 hours before and for at least 72 hours after palonosetron administration for a subset of patients.

5. The proposed delta of 15% is too high. We advise that it be lowered to 10%, and the sample size adjusted accordingly.

   (Note: After discussion, it was agreed that a delta of 15% was acceptable.)

6. All patients should be chemo naïve.

7. Efficacy data for Study 2330 show that results for the 0.3-1 mcg/kg doses did not differ significantly from the proposed Phase III doses (3 and 10 mcg/kg). Consider including the lower dose as an arm in the Phase III study. Please also describe how patients were distributed between the 0.3 and 1 mcg/kg doses.

8. Consider Poisson regression analysis, in addition to the planned logistic regression, for the secondary statistical analysis of the number of emetic episodes.

9. "Complete response" should be defined as no vomiting, no retching, no use of rescue medications, and – at the most- mild nausea.

- Regarding PALO-99-05:

Note: As indicated above, the firm has revised the protocol for Study PALO-99-05 so that it no longer provides for mandatory co-administration of Division representatives were unable to review the revised protocol in detail, however, they commented that if is included as part of the protocol, it should be administered i.v., at a standardized dose of mg.

1. The proposed study design will not show the contribution of to the prevention of emesis. This approach will be further considered when a more complete protocol is assessed by the Division.

2. Consider assessing palonosetron's effect on delayed emesis.

Please confirm the acceptability of the approach for calculating historical placebo control efficacy results involving moderately emetogenic chemotherapy for studies PALO-99-03 and PALO-99-04.

- **The use of a historical control is acceptable in principle, however, the adequacy of these particular trials must be assessed in detail.**

Minutes Preparer: /S/ 4/8/99

Chair Concurrence: /S/ - 4-8-99

Attachments/Handouts: [The sponsor will submit hard copies of all overheads that were presented at the meeting]

cc: Original IND [redacted]
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/McNeil
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-180/Goldkind
HFD-180/Choudary
HFD-180/Chopra
HFD-180/Duffy
HFD-180/Johnson
HFD-715/Al-Osh
HFD-870/Lee

Drafted by: mm\4/5/99\c:\mydocuments\cso\minutes[redacted]10-99-min.doc
Initialed by: LTalarico 4/5/99, 4/8/99
HGallo-Torres 4/6/99
final: April 8, 1999

MEETING MINUTES

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-372	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: Aloxi™ (palonosetron HCl injection)		Applicant: Helsinn Healthcare S.A.	
RPM: Brian Strongin, R.Ph., M.B.A.		HFD-180	Phone # 7-7473
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard () Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	July 27, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X (July 25, 2003)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X – November 1, 2002
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release () Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X (Submitted July 22, 2003)
• Original applicant-proposed labeling	X (Submitted September 26, 2002)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC Labeling Review – July 3, 2003); DMETS Tradename Reviews – July 16, 2002, September 13, 2002, and March 18, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X (Submitted June 25, 2003 and June 30, 2003)
• Reviews	X (See CMC Reviews #1 and #3)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X – March 10, 1999, April 19, 1999, and January 30, 2001(CMC)
• Pre-NDA meeting (indicate date)	X – April 10, 2002

• Pre-Approval Safety Conference (indicate date; approvals only)	X – (July 17, 2003)
• Other	X – October 18, 2001 (Statistics)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (July 21, 2003; July 25, 2003)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (July 2, 2003, July 8, 2003, July 22, 2003)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review #1
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X (July 3, 2003)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (June 24, 2003)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (June 9, 2003)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X [April 14, 2003 (DMF [redacted]) June 4, 2003, June 24, 2003, July 1, 2003, July 2, 2003 (DMF [redacted])
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (See CMC Review #1, June 4, 2003)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (May 29, 2003)
❖ Facilities inspection (provide EER report)	Date completed: (July 14, 2003) (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested

Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (July 10, 2003, July 11, 2003, July 23, 2003)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X (April 10, 2003, July 23, 2003)
❖ CAC/ECAC report	July 22, 2003

7/2/02

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-372

Name of Drug: Palonosetron HCl Intravenous Injection

Sponsor: Helsinn Healthcare S.A.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: September 26, 2002

Receipt Date: September 27, 2002

Filing Date: November 26, 2002

User-fee Goal Date: July 27, 2003 (if Standard)

Proposed Indication: [redacted]

Other Background Information: IND [redacted] for Palonosetron HCl Injection was submitted June 2, 1992 for prevention of cancer chemotherapy-induced nausea and vomiting. An End-of-Phase 2 Meeting was held March 10, 1999 and a follow-up teleconference to discuss clinical and biopharmaceutics issues was held April 19, 1999. A series of Special Clinical Protocol Assessment Requests were submitted by Helsinn beginning November 24, 1999 to discuss various aspects of the protocols for the proposed pivotal Phase 3 trials. Chemistry, manufacturing, and controls issues were discussed at a January 30, 2001 meeting to follow-up on the discussion at the End-of-Phase 2 meeting. A teleconference to discuss statistical issues was held October 18, 2001. A Pre-NDA meeting was held April 10, 2002.

Three pivotal Phase 3 trials have been submitted in support of the safety and efficacy of palonosetron for the proposed indication. PALO-99-03 and PALO-99-04 were submitted in support of the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. PALO-99-05 was submitted in support of the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. In addition, a Phase 2, dose-ranging study (Study 2330) conducted by a prior sponsor, Syntex, has also been submitted for the highly emetogenic indication.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	Y		Cover Letter.pdf
2. Form FDA 356h (original signature)	Y		356h Form.pdf
a. Establishment information	Y		Attachment to Form 356h on Volume 1.1, page 1
b. Reference to DMF(s) & Other Applications	Y		Attachment to Form 356h on Volume 1.1, page 1 (Drug Substance DMF info)
3. User Fee FDA Form 3397	Y		Volume 1.381, Section 18
4. Patent information & certification	Y		Volume 1.381, Sections 13 and 14
5. Debarment certification (Note: Must have a definitive statement)	Y		Volume 1.381, Section 16
6. Field Copy Certification	Y		Volume 1.381, Section 17
7. Financial Disclosure	Y		Volume 1.381, Section 19
8. Comprehensive Index	Y		Volume 1.1, Section 1.2
9. Pagination	Y		Each volume paginated separately
10. Summary Volume	Y		Volume 1.1
11. Review Volumes	Y		All review volumes have been distributed to the appropriate reviewers.

12. Labeling (PI, container, & carton labels)	Y		Volume 1.1, Section 2.0
a. unannotated PI	Y		Volume 1.1, Section 2.2
b. annotated PI	Y		Volume 1.1, Section 2.1
c. immediate container	Y		Volume 1.7, Section 4.3.11.1
d. carton	Y		Volume 1.7, Section 4.3.11.2
e. patient package insert (PPI)		N	Not provided
f. foreign labeling (English translation)		N	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	Y		CRT Folder (EDR)
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	Y		Volume 1.372 – 1.380, Section 12 (Archival copies will be provided for the clinical reviewer if necessary.)

Y=Yes (Present) N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	Y		Volume 1.92, Page 29
2. Foreign Marketing History	Y		Volume 1.1, Page 73
3. Summary of Each Technical Section	Y		Volume 1.1, Section 3.0
a. Chemistry, Manufacturing, & Controls (CMC)	Y		Volume 1.1, Page 74
b. Nonclinical Pharmacology/Toxicology	Y		Volume 1.1, Page 81
c. Human Pharmacokinetic & Bioavailability	Y		Volume 1.1, Page 108
d. Microbiology		N	N/A
e. Clinical Data & Results of Statistical Analysis	Y		Volume 1.1, Page 138
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	Y		Volume 1.1, Page 232
5. Summary of Safety	Y		Volume 1.1, Page 149
6. Summary of Efficacy	Y		Volume 1.1, Page 197

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	Y		Volume 1.92, Page 29
2. Controlled Clinical Studies			
a. Table of all studies	Y		Volume 1.92, Page 22
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	Y		See Attachment One
c. Optional overall summary & evaluation of data from controlled clinical studies		N	Not provided
3. Integrated Summary of Efficacy (ISE)	Y		Volume 1.94, Page 1
4. Integrated Summary of Safety (ISS)	Y		Volume 1.96, Page 1
5. Drug Abuse & Overdosage Information		N	N/A
6. Integrated Summary of Benefits & Risks of the Drug	Y		Volume 1.103, Page 4
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	Y		Efficacy: Subgroup analysis by gender and age only, Volume 1.94, page 111. Will request an analysis by race if necessary. Safety: Volume 1.96, page 183

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	Y		Volume 1.93, Page 187
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		N	Electronic Submission, review aids have not been requested. The information listed below has been provided in the EDR where noted.
a. Proposed unannotated labeling in MS WORD	Y		(EDR) Labeling Folder, Proposed Labeling.doc
b. Stability data in SAS data set format (only if paper submission)	Y		(EDR) CMC Folder
c. Efficacy data in SAS data set format (only if paper submission)	Y		(EDR) CRT Folder
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		N	Will request if necessary
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)	Y		(EDR) Pharm/Tox Folder
3. Exclusivity Statement (optional)		N	Not provided

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

From an administrative standpoint, this application is fileable. A 45-Day planning/filing meeting has been scheduled for November 6, 2002. An analysis of efficacy data by race will be requested if necessary.

ATTACHMENTS
Attachment #1