CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Chemistry Review(s)

NDA 21-372

Aloxi (palonosetron HCl) Injection 25 mg/5 mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Helsinn Healthcare S.A.

Indication: Prevention of accute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer therapy

Presentation: 25 mg/5mL —

EER Status: Acceptable 14-JUL-2003

Consults: ODS – Tradename: Aloxi- acceptable 9-JAN-2003
Statistics – none
EA – no consult - waiver requested – granted

CMC Phase IV Commitments: none

The original NDA was received 26-SEP-2002

The **drug substance** is manufactured by:

Helsinn Advanced Synthesis
Biasca, SZ

DMF 16,063

The synthetic process is — from well characterized commercially available starting materials. The manufacturing process is well defined and in-process controls are adequate.

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. Impurities and degradation products were well studied and are adequately controlled. A re-test period of 12 months is supported by submitted stability data – the applicant had requested a — re-test period. The stability testing protocol is considered adequate.

Conclusion
Drug substance is acceptable.

The **drug product** is formulated as an aqueous solution with mannitol, buffering agents with pH adjustment ——————— 25 mg/5 mL.

Manufacturer:

SP Pharmaceutical
Albuqueque, NM

The manufacturing method is a standard process for a parenteral product with ——— sterilization. The proposed regulatory specifications are acceptable including impurities. The proposed —— expiry is not supported with suffucient data – the 18 months of data provided support a 24 month expiry. The stability testing protocol is considered adequate.

The overall Compliance recommendation is acceptable as of 14-JUL-20003

All associated DMFs are acceptable.

Conclusion
Drug product is acceptable

Overall Conclusion
From a CMC perspective the application should be approved.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
7/18/03 11:43:39 AM
CHEMIST

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MEMO

To: NDA 21-372 (Palonosetron Injection)

From: Marie Kowblansky, PhD

Through: Ali Al-Hakim, PhD, Acting Team Leader HFD-180

Brian Strongin, Project Manager, HFD-180

Date: 6/30/03

Subject: Immediate Container and Carton Labeling

The submission from August Consulting (sponsor: Helsinn Healthcare SA), dated June 25, 2003, provides FAXed copies of the immediate container and carton labels for the above product.

Drug vial:

The label gives the product name, Aloxi™ palonosetron HCl injecton, the amount of palonosetron per milliliter and per 5 milliliters, a statement that the product is for intravenous single-use, lot number, expiration date, and the distributor's name. The applicant was contacted by telephone on June 30th with the request that the storage conditions be added to the label. The applicant agreed with our request. However, in view of the small size of the label, the phrase "——" will be deleted from the label, and the storage statement will read "protect from light" and "Store at 20°C-25°C (60°F-77°F)", omitting the phrase "——". In view of the limited space on the label and the fact that all the omitted statements are included on the carton label, this is considered acceptable.

CARTON LABEL

The carton label contains the same information as on the drug vial, the complete storage statement, lot number, expiration date, and the full composition of the drug product, and identifies the distributor. This is considered acceptable.

SHIPPER CARTON LABEL (2-1-127)

The carton label contains the product name, concentration of the active in the product, lot number, expiration date, complete storage statement and manufacturer and distributor. The box also indicates the number of single-use vials that are found in the box. This is considered acceptable.

In a July 1st FAX, the applicant confirms the agreements described above from the June 30th teleconference.

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/s/

Marie Kowblansky
7/1/03 10:52:40 AM
CHEMIST

Ali Al-Hakim
7/1/03 10:57:26 AM
CHEMIST

NDA 21-372

Palonosetron Hydrochloride
Intravenous Injection, 0.25 mg
(0.05 mg/mL)

Helsinn Healthcare SA

Marie Kowblansky, Ph.D.
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Table of Contents

A. Labeling & Package Insert ..... see Review #1

B. Environmental Assessment Or Claim Of Categorical Exclusion ..... see Review #1

III. List Of Deficiencies To Be Communicated ..... none

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ON ORIGINAL

Chemistry Review Data Sheet

1. **NDA 21-372**

2. **REVIEW #:** 1

3. **REVIEW DATE:** May 23, 2003

4. **REVIEWER:** Marie Kowblansky, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
None	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	September 26, 2003
BC	November 21, 2003
BC	April 9, 2003
BC	June 13, 2003
BC	June 20, 2003

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Helsinn Healthcare SA
Address:	Via Pian Scairolo 6912 Pazzallo (Lugano) Switzerland
Representative:	Craig Lehmann, Pharm.D.
Telephone:	(512) 347-1755
Fax:	(512) 347-9375

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride

b) **Non-Proprietary Name (USAN):** palonosetron hydrochloride
c) **Code Name/# (ONDCS only):** NA
d) **Chem. Type/Submission Priority** (ONDC only):
- **Chem. Type:** 1
- **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:**

10. **PHARMACOL. CATEGORY**: antiemetic and antinauseant

11. **DOSAGE FORM:** sterile solution

12. **STRENGTH/POTENCY**: 0.05 mg/mL; 0.25 mg/vial

13. **ROUTE OF ADMINISTRATION**: intravenous injection

14. **Rx/OTC DISPENSED**: __√__ **Rx** ___ **OTC**

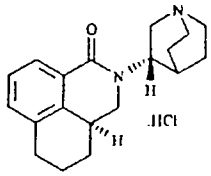
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:**

_____SPOTS product – Form Completed

__√__ Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

CHEMICAL NAME: (3a*S*)-2-[(*S*)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride



MOLECULAR FORMULA: $C_{19}H_{24}N_2O.HCl$
MOLECULAR WEIGHT: 332.87

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16063	1	Helsinn Advanced Synthesis	Drug substance	1	Adequate	June 24, 2003	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Palonosetron hydrochloride

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable	4/10/03	Milton. Fan
EES	Pending	6/24/03	Su Chih Lee
Pharm/Tox	Pending		
Biopharm	Approval		
LNC	Not Applicable		----
Methods Validation	Pending		
DMETS	pending		
EA	Not required*	5/23/03	M. Kowblansky
Microbiology	Approval	5/28/03	J. McVey

*The applicant appropriately claims categorical exclusion on the basis that the concentration of the active moiety will not exceed 1 ppb at the point of entry into the aquatic environment.

The Chemistry Review for NDA 21-372

The Executive Summary

I. Recommendations

A. From the chemistry perspective, this application may be Approved pending

1. completion of a satisfactory GMP inspection. (Inspection scheduled to begin June 26th)

2. a written decision by the toxicology reviewer that impurities ——— and ——— are qualified to be present at the relatively high levels of ~ , as proposed by the applicant. (In a palonosetron team meeting held June 24, 2003, Dr. Y Chopra indicated that the Pharm./Tox. Review will indicate that the proposed levels are considered toxicologically qualified.)

B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable** – None required

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active drug substance is palonosetron hydrochloride. It is synthesized as the (S,S)-stereoisomer and contains two chiral centers, with four potential stereoisomers or two diastereomeric pairs of enantiomers. The enantiomeric purity of the final product is assured by control over the enantiomeric purity of the starting material and of the intermediates. No racemization has been observed (by ———) at either of the two stereocenters, either under synthetic conditions or under stressed stability testing.

The applicant proposes relatively high specification limits of ~ % for two of the impurities ——— At these levels, they will have to be toxicologically qualified per ICH Guidelines. Consequently, the acceptability of these specification limits will be decided when the toxicology review has been completed.

The proposed drug product is a ——— sterilized buffered solution for IV administration. It is supplied in 5 mL vials containing 0.25 mg palonosetron (as the hydrochloride), mannitol, disodium edetate, and citrate buffer in water for injection. Sodium hydroxide or hydrochloric acid are used for adjustment to pH 5. It is packaged in ——— glass single-dose vials. The product has been found to be unstable when exposed to light. Consequently, the vial is packaged in an outer carton, which serves to protect it from light, resulting in a stable product. Based on the 18-month primary stability data that were submitted for product manufactured at the current manufacturing site, a 24 month expiration is appropriate for the product at the present time.

NOTE: The applicant makes repeated references to higher concentration formulations, particularly — mg/mL, and provides data for these formulations. Since this NDA is for a single product that contains 0.05 mg/mL of palonosetron, the information regarding the higher dose formulations has not been carefully reviewed, but was used as supporting information, when warranted.

B. Description of How the Drug Product is Intended to be Used

The dosing instructions call for infusing intravenously over 10 to 30 seconds.

C. Basis for Approvability or Not-Approval Recommendation

At this time, this application is judged to be Approvable from the CMC perspective, pending resolution of the issue cited above (under Recommendations).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Marie Kowblansky, Ph.D.
ChemistryTeamLeader: Liang Zhou, Ph.D.
ProjectManager: Brian Strongin

C. CC Block

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/s/

Marie Kowblansky
6/24/03 04:39:09 PM
CHEMIST

Liang Zhou
6/24/03 05:03:27 PM
CHEMIST
Pending EER.

NDA 21-372

Palonosetron Hydrochloride
Intravenous Injection, 0.25 mg
(0.05 mg/mL)

Helsinn Healthcare SA

Marie Kowblansky, Ph.D.
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

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Chemistry Review Data Sheet

1. **NDA 21-372**

2. **REVIEW #**: 1

3. **REVIEW DATE**: May 23, 2003

4. **REVIEWER**: Marie Kowblansky, Ph.D.

5. **PREVIOUS DOCUMENTS**:

Previous Documents	Document Date
None	

6. **SUBMISSION(S) BEING REVIEWED**:

Submission(s) Reviewed	Document Date
Original	September 26, 2003
BC	November 21, 2003
BC	April 9, 2003

7. **NAME & ADDRESS OF APPLICANT**:

Name:	Helsinn Healthcare SA
Address:	Via Pian Scairolo 6912 Pazzallo (Lugano) Switzerland
Representative:	Craig Lehmann, Pharm.D.
Telephone:	(512) 347-1755
Fax:	(512) 347-9375

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride

b) **Non-Proprietary Name (USAN)**: palonosetron hydrochloride
c) **Code Name/# (ONDCS only):** NA
d) **Chem. Type/Submission Priority** (ONDC only):
- **Chem. Type:** 1
- **Submission Priority**: S

9. **LEGAL BASIS FOR SUBMISSION**:

10. **PHARMACOL. CATEGORY**: antiemetic and antinauseant

11. **DOSAGE FORM:** sterile solution

12. **STRENGTH/POTENCY**: 0.05 mg/mL; 0.25 mg/vial

13. **ROUTE OF ADMINISTRATION**: intravenous injection

14. **Rx/OTC DISPENSED**: __√__ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:**
_____SPOTS product – Form Completed

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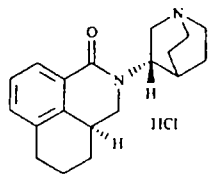
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

CHEMICAL NAME: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1<u>*H*</u>-benz[*de*]isoquinoline hydrochloride



MOLECULAR FORMULA: $C_{19}H_{24}N_2O.HCl$
MOLECULAR WEIGHT: 332.87

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16063	1	Helsinn Advanced Synthesis	Drug substance	1	Inadequate	March 29, 2003	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Palonosetron hydrochloride

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	NA		
LNC	Pending		
Methods Validation	Pending		
DMETS	pending		
EA	Not required*	5/23/03	M. Kowblansky
Microbiology	pending		

*The applicant appropriately claims categorical exclusion on the basis that the concentration of the active moiety will not exceed 1 ppb at the point of entry into the aquatic environment.

APPEARS THIS WAY
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The Chemistry Review for NDA 21-372

The Executive Summary

I. Recommendations

A. From the chemistry perspective, this application is Approvable, pending

1. Resolution of the issues cited in the Draft Deficiency letter, the most notable of which is a tightening of impurity specifications to reflect the actual manufacturing history and levels found in supplies used in clinical trials.

2. Resolution of the deficiencies in the drug substance DMF. The deficiencies have already been communicated to the DMF holder.

3. A decision by the toxicology reviewer that impurities ——— and ——— are qualified to be present at the relatively high levels proposed by the applicant.

B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable** – No post-approval commitments are required at the present time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active drug substance is palonosetron hydrochloride. It is synthesized as the (S,S)-stereoisomer and contains 2 chiral centers, with four potential stereoisomers or two diastereomeric pairs of enantiomers. The enantiomeric purity of the final product is assured by control over the enantiomeric purity of the starting material and of the intermediates. No racemization has been observed ——— at either of the two stereocenters, either under synthetic conditions or under stressed stability testing.

The applicant proposes relatively high specification limits of —% for two of the impurities ——— At these levels, they will have to be toxicologically qualified per ICH Guidelines. Consequently, the acceptability of these specification limits will be decided when the toxicology review has been completed.

The proposed drug product is a ——— sterilized buffered solution for IV administration. It is supplied in 5 mL vials containing 0.25 mg palonosetron (as the hydrochloride), mannitol, disodium edetate, and citrate buffer in water for injection. Sodium hydroxide or hydrochloric acid are used for adjustment to pH 5. It is packaged in — glass single-dose vials. The product has been found to be unstable when exposed to light. Consequently, the vial is packaged in an outer carton, which serves to protect it from light, resulting in a stable product.

NOTE: The applicant makes repeated references to higher concentration formulations, particularly —— mg/mL, and provides data for these formulations. Since this NDA is for a single product that contains 0.05 mg/mL of palonosetron, the information regarding the higher dose formulations has not been carefully reviewed, but was used as supporting information, when warranted.

B. Description of How the Drug Product is Intended to be Used

The dosing instructions call for infusing intravenously over 10 to 30 seconds.

C. Basis for Approvability or Not-Approval Recommendation

At this time, this application is judged to be Approvable based on the issues cited above (under Recommendations).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Marie Kowblansky, Ph.D.
ChemistryTeamLeader: Liang Zhou, Ph.D.
ProjectManager: Brian Strongin

C. CC Block

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/s/

Marie Kowblansky
6/3/03 06:59:12 PM
CHEMIST

Liang Zhou
6/4/03 05:46:53 PM
CHEMIST

[redacted] can be set limit to less than [redacted] based on DS specifications in IR request #1. Other imputies can be also set up low limits according to DS specification in IR #2.

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MEMO

To: NDA 21-372 (Palonosetron Injection)

From: Marie Kowblansky, PhD

Through: Liang Zhou, PhD, Team Leader HFD-180

Brian Strongin, Project Manager, HFD-180

Date: 7/14/03

Subject: Office of Compliance Manufacturing Facility Recommendation for NDA 21-372

On July 14, 2003 the Office of Compliance issued a recommendation that all facilities associated with the manufacture of Palonosetron Injection, 25mg/mL are Acceptable. Their summary report is reproduced below:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21372/000 Sponsor: HELSINN HEALTHCARE SA

Org Code : 180 6912

Priority : 1S PAZZALLO, LUGANO, SZ

Stamp Date : 27-SEP-2002 Brand Name : PALONESETRON HCL 0.5MG/5ML

PDUFA Date : 27-JUL-2003 Estab. Name:

Action Goal : 25-JUL-2003 Generic Name: PALONOSETRON HCL 0.5MG/5ML

District Goal: 26-MAY-2003 Dosage Form: (INJECTION)

Strength : 0.05 MG/ML

FDA Contacts: B. STRONGIN Project Manager (HFD-180) 1-827-7310

M. KOWBLANSKY Review Chemist (HFD-180) 1-827-7310

L. ZHOU Team Leader (HFD-180) 1-827-1251

Overall Recommendation: ACCEPTABLE on 14-JUL-2003by S. ADAMS (HFD-3) 301-827-9051

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/s/

Marie Kowblansky
7/14/03 01:19:41 PM
CHEMIST

Liang Zhou
7/14/03 02:24:35 PM
CHEMIST